United States Court of Appeals

for the Second Circuit

JOINT APPENDIX

76-6135

In The

United States Court of Appeals

For The Second Circuit

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR, CO., INC.,

Plaintiffs-Appellants,

vs.

F. DAVID MATHEWS, Secretary of Health, Education and Welfare and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants-Appellees.

On Appeal from the United States District Court for the Southern District of New York.

JOINT APPENDIX

Volume I, 1a - 314a

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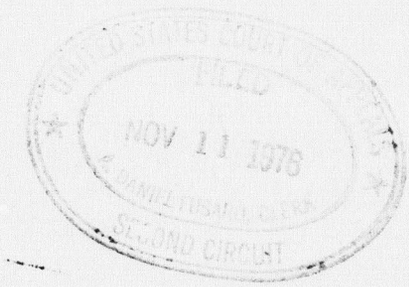

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DOCKET ENTRIES

CIVIL DOCKET

UNITED STATES DISTRICT COURT

JUDGE FRANKEL

Jury demand date:

. C. Form No. 106 Rev.

73 C 3448

TITLE OF CASE	ATTORNEYS
THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.	For plaintiff: Bass & Ullman 342 Madison Ave. New York, N.Y. 10017 ~~687-3880~~
-v-	Bass Ullman & Lustigman 747 Third Ave. NYC 10017 751-9494
CASPER W. WEINBERGER, Secretary of Health, Education and Welfare and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs	For defendant:

STATISTICAL RECORD	COSTS	DATE	NAME OR RECEIPT NO.	REC.	DISB.
J.S. 5 mailed x	Clerk	8/6/73	Gen'l	15 —	
		8/6/73	Treas		15 —
J.S. 6 mailed ~~x~~ Closed ~~REVIEWED 3-7-75~~	Marshal	8/6/73	Bass	5 —	
		8/6/73	Ullm		5 —
Basis of Action: declaratory judgmt. Vitamin A Preparations etc. 28 U.S.C. 1331(a) $10,000.	Docket fee	8/28/73	BDS	5 —	
		8/28/73	Treas		5 —
	Witness fees				
Action arose at:	Depositions				

onal Nutritional Foods Et.ano. v Casper W. Weinberger

JUDGE FRANKEL

73 CIV. 3448

PROCEEDINGS	Date Order or Judgment Noted
Filed complaint and issued summons	
Filed pltff's afdvt.& notice of motion for preliminary injunction	
Filed pltff's memorandum of law in support of pltff's motion for injunction	
Filed defts Order to Show Cause: Re: Adjourn Preliminary Injunction. ret. Frankel J.	
Filed memo endorsed on Order To Show Cause this date, Motion adjourned until 9-10-73 in room 128 or to such other time and place J. Frankel may fix. So Ordered, Wyatt, J.	
73 Filed summons with marshals return, Served Lasper W. Inberger Sec. H.E.W. on 8-9-73 als o served Alexander M. Schmidt, Comm. of FDA on 8-9-73.	
73 Filed certificate of Alexander M. Schmidt, M.D. re: 45 volumes of documents.	
73 Filed Govt's notice of motion re: dismissal before Frankel J. on 9-17-73	
73 Filed deft's Memo in opposition to pltff's motion for a preliminary injunction and in support of deft's motion to dismiss.	
73 Filed appendix to deft's Memorandum of Law.	
Filed affidavit of Joseph John Vitale.	
Filed reply memorandum in support of pltffs motion for a preliminary injunction.	
Filed pltffs supplemental memorandum.	
Filed pltffs supplemental appendix.	
Filed affdvt. of Naomi L. Reice, AUSA, dated 9-19-73.	
Filed deft's Memorandum in response to pltff's supplemental Memorandum.	
Filed Memorandum-Opinion # 39849--in short, the public interest in health quite overwhelms the financial concerns plaintffs urge-beyond that, the likelihood that pltffs. will succeed in this action seems negligible- there are, then, no grounds for, and powerful grounds against, a preliminary injunction. pltff's motion is denied. So ordered FRANKEL, J.	
Filed pltff's notice of appeal to USCA from order denying pltff's motion for preliminary injunction entered 9-25-73. Mailed copy to:USA SDNY	
Filed certification of record on appeal.	
Filed pltffs Notice to take deposition of A. M. Schmidt. on 10-15-73.	
Filed defts order and order to show cause why an order should not be entered pursuant to rule 26(c)vacating a notice of deposition..Ordered that pltff is restrained from taking deposition of deft Alexander M.Schmidt..Ret.10-26-73 9:30a.m.	
Filed pltffs.' affdvt. by Milton A. Bass in opposition to defts' motion to vacate as indicated.	
Filed stip & order that oral argument on defts' motion to quash the deposition notice for Alexander M. Schmidt is adjourned until a mutually convenient date following a decision by the Court of Appeals as indicated. So ordered FRANKEL, J.	
Filed transcript of proceedings of 9-13-73	
Filed affdvt. of Naomi L.Reice, AUSA & Exhibits (Vols. I & II)attached.	
Filed supplemental affdvt.in opposition to defts motion to vacate notice of deposition.	
Filed defts' supplemental memorandum.	
Filed pltffs' Memorandum of Law in opposition to defts' motions for summary judgment and to vacate the notice of deposition.	
Filed true copy of USCA mandate with opinion attached- order of District Court is affirmed with costs to be taxed against the appellants in the sum of $ 598.37 - Docketed as Judgment #74,187 on 2-19-74	
Filed Opinion # 40555- on 10-1-73, regulations of the Food and Drug Administration became effective requiring that preparations of Vitamin A and Vitamin as indicated be restricted to prescription sale and that such vitamins be labeled accordingly. Plttffs., involved in the manufacture, distribution, and sale of Vitamin A and D, filed suit on 8-6-73, seeking declaratory and injunctive relief against the regulations.	(N)

CONTD ON NEXT PAGE #2

DATE	PROCEEDINGS
5-74 (Cont'd)	-- Opinion # 40555----defts. have now moved for summary judgment dismissing the complaint. The reasons are stated in opinion- pltffs' notice of deposition is vacated. defts' motion for summary judgment is granted. The complaint is dismissed. So ordered- FRANKEL, J. (m/n)
Apr. 8-74	Filed Judgment- ordered that defts. Caspar W. Weinberger, Secretary of H.E.W., and Alexander M. Schmidt, Commissioner of Food & Drugs, have judgment against the pltff. The National Nutritional Foods Association and Solgar Co., Inc. dismissing the complaint. Clerk (m/n)
May 16-74	Filed pltffs notice of appeal from the final order dismissing the complaint, entered on 4-6-74. Copy mailed to: U.S. Atty. Entered 5-17-74
June 24-74	Filed notice that the record on appeal has been certified and transmitted to the USCA on 6-24-74.
March 7-75	Filed true copy of USCA order with opinion-remanding action to District Court for further proceedings not inconsistent with the opinion of this court. (m/n)
Mar.28-75	Filed affdvt.of Alexander M.Schmidt,M.D.Commissioner of Food and Drugs...
Mar.28-75	Filed Govt's memorandum submitted in connection with the direction of remand of second circuit...
May 30-75	Filed pltffs' memorandum in response to affdvt. of Alexander M. Schmidt, Commissioner of Food and Drugs.
May.30-75	Filed additional affdvt. of Allen Skolnick in connection with label copy and potencies of vitamin A & D products.
June 17-75	Filed Government's reply memorandum
Nov.06-75	Filed Govt'sAffidavit re:promulgation of regulations,etc.by Stephen Hull McNamara.
Nov.06-75	Filed Government's Memorandum on the record of Vitamin A and D Regulations.
2-20-76	Filed deft's affdvt (Alexander M. Schmidt, M.D.), Comm. of Food & Drugs, re regulation of certain drugs.
3-3-76	Filed pltffs memorandum in response to direction of the Court in chambers on 9-4-75.
4-9-76	Filed Govt's reply memo re 4-75 conference.
7-2-76	Fld Opinion #41703.....The Complt is dismissed. So Ordered...Frankel,J. mn
7-19-76	Filed Transcript of record of proceedings, dtd 5-28-76
8-14-76	Filed pltffs notice of appeal to the USCA from the order of summary judgment ent. 7-2-76, from each & every part of said order. Copy sent to Naomi Rice Buchwald, Assistant U.S. Attorney, Southern District of N.Y., 1 St. Andrews Plaza, New York, N.Y. 10007.
9-9-76	Filed Transcript of Record of Proceedings dtd 6-1-76.
9-29-76	Filed notice that original record on appeal has been Certified & transmitted to the USCA.

COMPLAINT

UNITED STATES DISTRICT COURT (Filed August 6, 1973)
SOUTHERN DISTRICT OF NEW YORK

----------x

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,

Plaintiffs,

-against-

COMPLAINT

CASPER W. WEINBERGER, Secretary of Health, Education and Welfare and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

----------x

STATEMENT AS TO JURISDICTION AND VENUE

1. This is an action for (a) a declaratory judgment that the provisions of the regulations entitled "Vitamin A Preparations for Oral Use as Drugs" and "Vitamin D Preparations for Oral Use as Drugs" at 21 CFR §§3.94 and 3.95 published in the Federal Register on August 2, 1973 at 38 F.R. 20723-20725 (hereinafter referred to as the "Vitamin A and D Regulations"), are not in accordance with law, are in excess of the statutory jurisdiction, authority and limitations of the defendants and are short of statutory right, and (b) for injunctive and other relief.

2. Jurisdiction of this Court is invoked pursuant to 28 U.S.C. §§1331(a) and 1337. The matter in controversy exceeds the sum or value of $10,000.00, exclusive of interest and costs, and the action arises under the laws of the United States, namely the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §301 et seq.

and also the Administrative Procedure Act, 5 U.S.C. §1001 et seq.

3. This action is authorized by 28 U.S.C. §§2201 and 2202 and 5 U.S.C. §1009. The plaintiffs are suffering legal wrong because of the final agency action of the Commissioner of Food and Drugs in promulgating the Vitamin A and D regulations and are aggrieved by such action. This is a case of actual controversy which requires a declaration with respect to the invalidity of said regulations as alleged in this complaint.

4. Venue in this judicial district is proper by virtue of 28 U.S.C. §1391(e)4.

PARTIES

5. Plaintiff Solgar Co., Inc. is a New York corporation with its principal place of business in this district at 92 East 10th Street, New York, New York, and engages in the manufacture, distribution and sale in interstate commerce of vitamins and dietary supplements. Plaintiff National Nutritional Foods Association is composed of business concerns located in New York State and throughout the United States, including manufacturers, wholesalers and retailers of vitamins and dietary supplements. The plaintiffs join as such in this one action since they assert rights to relief in respect of and arising out of the same transaction and occurrence and questions of law common to both of them will arise in this action.

6 Defendant Casper W. Weinberger is the Secretary of Health, Education and Welfare and is the officer charged with the administration of the Federal Food, Drug, and Cosmetic Act. He is authorized by 21 U.S.C. §371 to promulgate regulations for

the efficient enforcement of the Act. Defendant Alexander Schmidt is the Commissioner of Food and Drugs and is responsible for the supervision of the Food and Drug Administration. The Secretary of Health, Education and Welfare has purported to assign to the Commissioner of Food and Drugs the functions vested in the Secretary under the Federal Food, Drug and Cosmetic Act. The defendant Commissioner is the officer who, purportedly under color of legal authority, promulgated the Vitamin A and D regulations.

FACTUAL ALLEGATIONS

7. The Vitamin A and D regulations promulgated by the defendant Commissioner declare that preparations which contain Vitamin A in excess of 10,000 International Units per dosage unit are drugs and limit such items to sale by prescription only. The same limitations are applied to preparations containing Vitamin D in excess of 400 International Units per dosage unit. Preparations labeled contrary to the regulations are made subject to regulatory proceedings as of October 1, 1973.

8. The Commissioner of Food and Drugs set forth the purported rationale for the above limitations at 37 Federal Register 26618-26620, December 14, 1972, by asserting that toxicity of Vitamins A and D at high levels required the dosage limitations and classifications as ultimately promulgated in the Vitamin A and D regulations. As scientific support for his position, the Commissioner cited supposed scientific information and literature regarding Vitamin A and D toxicity which had been listed with the Hearing Clerk of the Department of Health, Education and Welfare.

9. The body of scientific knowledge relating to Vitamin A

and D toxicity absolutely demonstrates that the dosage limitations and classifications in the Vitamin A and D regulations are totally without scientific foundation or merit. Neither the general body of scientific knowledge nor the literature cited by the Commissioner provide any factual or medical basis for the promulgation of the Vitamin A and D regulations. These regulations are arbitrary, unjust, an abuse of the regulatory power prescribed by Congress and beyond the legal authority of the Commissioner of Food and Drugs and the Secretary of Health, Education and Welfare.

10. The provisions of the Vitamin A and D regulations are additionally beyond the scope of any legal authority in that they arbitrarily and without any statutory authority classify certain common food items as drugs and arbitrarily and without statutory authority require them to be dispensed only by prescription.

11. The promulgation of the Vitamin A and D regulations is additionally beyond the scope of any legal authority in that they involve questions of scientific and medical knowledge and facts which were decided unilaterally and arbitrarily by the defendant Commissioner without any public hearings wherein competent testimony could have been adduced to determine such factual questions in accordance with due process of law.

12. Plaintiff Solgar Co., Inc. and the members of plaintiff National Nutritional Foods Association are aggrieved by the promulgation of the Vitamin A and D regulations in that their manufacture, distribution and sale of products containing Vitamin A and D will be unnecessarily and unlawfully restricted

to a very large degree by the requirement of sale by prescription at the specified dosage levels. Plaintiffs are presently aggrieved and injured by the Vitamin A and D regulations in that their production, distribution and inventory patterns are immediately affected. The enforcement of the Vitamin A and D regulations after October 1, 1973 , even for a temporary period during the pendency of this action, will cause great and irreparable damage to plaintiffs from the nationwide loss of sales on their Vitamin A and D products.

13. Plaintiffs have no prompt, adequate and effective remedy at law, and this action is the only means available to them for the protection of their rights and for the protection against the immediate, real and substantial damage and injury which plaintiffs face.

WHEREFORE, Plaintiffs pray that this Court:

(1) Issue a judgment declaring that the Vitamin A and D regulations are not in accordance with law, are in excess of statutory jurisdiction, authority and limitations of the defendants, and contrary to the statutory provisions on which they purport to be based, and are null and void and of no effect.

(2) Enjoin and restrain the defendants and all persons acting under their direction and authority, or in active concert or participation with them, from enforcing or causing to be enforced, or from attempting to enforce or to cause to be enforced, by any administrative action or civil or criminal proceeding, the Vitamin A and D regulations alleged herein as being null and void

and of no effect.

(3) Issue a preliminary injunction enjoining and restraining the defendants and said other persons from enforcing or causing to be enforced or attempting to enforce or to cause to be enforced, by any administrative action or civil or criminal proceeding or otherwise, said provisions of the Vitamin A and D regulations and to preserve the status and rights of plaintiffs pending conclusion of this action.

(4) Grant such other and further necessary or proper relief as to this Court may seem just and proper.

Dated: New York, New York
August 6, 1973

BASS & ULLMAN

By: _____
(A Member of the Firm)

Office & P.O. Address
342 Madison Avenue
New York, New York 10017
(212) 697-3880

BEST COPY AVAILABLE

MOTION FOR PRELIMINARY INJUNCTION

UNITED STATES DISTRICT COURT (Filed August 15, 1973)
SOUTHERN DISTRICT OF NEW YORK

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,

Plaintiffs,

-against-

CASPER W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

Index No. 73 Civ. 3448

MOTION FOR PRELIMINARY INJUNCTION

Upon the complaint herein and the annexed affidavits of Robert Ullman, Harold Rosenberg, D.O., Carlton Fredericks, Allen Skolnick and Philip Pollack, and upon the Agriculture Handbook No. 8 prepared by the Agricultural Research Service, U.S.D.A., entitled Composition of Foods, plaintiff will move this Court on August 27th, 1973 for a preliminary injunction enjoining the defendants herein, their agents, servants, employees and attorneys and all persons in active concert and participation with them, from enforcing or causing to be enforced, or attempting to enforce or to cause to be enforced, the "Vitamin A and D Regulations" at issue herein, on the grounds that

(1) Unless restrained by this court defendant will perform the acts referred to;

(2) Such action by the defendant will result in irreparable injury, loss and damage to the plaintiffs, as more particularly appears in the complaint and the affidavits of Allen Skolnick and Philip Pollack, attached hereto;

(3) The issuance of a preliminary injunction herein

will not cause undue inconvenience, loss or injury to defendant, or to the public, but will prevent irreparable injury to plaintiffs.

Dated: New York, New York
August 15, 1973

BASS & ULLMAN

Attorneys for Plaintiffs
Office & P.O. Address
342 Madison Avenue
New York, New York
(212) 697-3880

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

(Filed August 15, 1973)

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,

Plaintiffs,

-against-

CASPER W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

Index No. 73 Civ. 3448

AFFIDAVIT

STATE OF NEW YORK)
) SS.:
COUNTY OF NEW YORK)

ALLEN SKOLNICK, being duly sworn, deposes and says:

1. I am the Vice-President of plaintiff Solgar Co., Inc. which is a member of the plaintiff National Nutritional Foods Association, and I make this affidavit in support of plaintiffs' motion for preliminary injunction restraining the defendants herein from enforcing the order published in the Federal Register at 38 F.R. 20723-20725, known as the "Vitamin A and D Regulations."

2. For the past 26 years, Solgar Co., Inc. has been engaged in the formulation, packaging, distribution and sale of various vitamin and dietary food supplement products. Our products are sold nationwide both under our own and under private label and the current annual volume of our sales is approximately two million dollars. Other members of the NNFA, located through-

out the United States, are similarly engaged in such activities at the manufacturer, wholesaler, distributor, and retailer levels.

3. The Vitamin A and D regulations promulgated by the defendant Commissioner of Food and Drugs, declare that any product containing more than 10,000 I.U. of Vitamin A per dosage unit and more than 400 I.U. of Vitamin D per dosage unit, are drugs which may be purchased by the consumer only by prescription.

4. Solgar Co., Inc. is currently distributing approximately 150 products containing Vitamin A and/or Vitamin D which are affected by the new regulations. Our annual sales of these products total approximately three quarters of a million dollars, accounting for approximately 40 percent of our total sales.

5. The new regulations have already wrought total havoc with our company's current production, distribution and inventory planning. After October 1, 1973, the Vitamin A and D regulations will prohibit us from continuing to manufacture, label, and ship in interstate commerce the variety of products mentioned above without drastically changing their composition. In addition, all of our advertising, promotional and informational material and literature will have to be discarded and revised in order to advise the customer that he will no longer be getting the dosages presently found in our products. Thus, at the very outset we will immediately be faced with relabeling and reformulation costs totaling in the area of $50,000 in order to make the above changes. It is clear to us that if the Vitamin A and D regulations are enforced, our company faces the loss of

a substantial portion of the $750,000 sales of products containing Vitamin A and D. Moreover, the reputation, good will and integrity established by the sale of our products for over 20 years will immediately be thrown into question By the sudden forced change in formulation. The effect of the instant regulation would be to jeopardize our entire product line by imposing new restrictions and creating totally new marketing conditions which are completely out of line with reality.

6. The FDA claims of health hazards with respect to the current Vitamin A and D dosages available in the marketplace are contradicted by our marketing experience. Although some of our products contain dosages of Vitamin A in excess of 10,000 I.U. and Vitamin D in excess of 400 I.U., we have never received any report of adverse effects from the use of our products. These types of products and dosages have been on the market for over 30 years and have been used by millions of consumers. I respectfully request that in order to maintain the status quo and to avoid the irreparable injury to our company as outlined above, the defendants in this case be preliminarily enjoined from enforcing the Vitamin A and D regulations so that the plaintiffs herein can have an effective remedy upon their presentation to the court of evidence demonstrating that the new regulations are medically, scientifically and factually unsound and unreasonable, as well as beyond the scope of the authority of the Commissioner of Food and Drugs.

ALLEN SKOLNICK

Sworn to before me this

14th day of August, 1973.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

(Filed August 15, 1973)

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,

Plaintiffs,

-against-

CASPER W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

Index No. 73 Civ. 3448

AFFIDAVIT

STATE OF NEW JERSEY)
) SS.:
COUNTY OF BERGEN)

PHILIP POLLACK, being duly sworn, deposes and says:

I am the President of Leeds-Dixon Laboratories Corp., Moonachie, New Jersey. Leeds-Dixon is a member of plaintiff National Nutritional Foods Association and is a wholly owned subsidiary of Iroquois Brands, Ltd., a New York corporation whose stock is publicly held.

Leeds-Dixon is a manufacturer and distributor of a variety of products, including dietary supplements of vitamins and minerals under the trade names Schiff Bio Foods, Basic Organics and Natura Brands. This vitamin business was started by Eugene Schiff over 25 years ago. Today our products are sold on a nationwide basis. In addition to manufacturing vitamin products under our own labels, we manufacturer and package formulations under private label for distribution throughout the country, primarily in retail Health Food Stores, and we further

manufacture and sell in bulk vitamin and mineral products for re-packaging and sale by other companies.

Considering our own label products, private label products, and bulk sales, the formulations we manufacture and sell include Vitamin A and D in over 450 products. I would estimate the gross annual sales of such products to be in excess of one million dollars.

On August 2, 1973, the Food and Drug Administration published regulations which for the first time in our more than twenty-five years in business would allow products containing more than 10,000 I.U. Vitamin A and 400 I.U. Vitamin D to be sold on prescription only. All products labeled after October 1, 1973 are required to be in compliance with these regulations. An immediate consequence of such regulations would be that products which we have sold for as long as twenty-five years as dietary food supplements would have to be either discontinued or re-formulated; advertising, product labels, catalogs and other labeling and promotional material currently being used would have to be discarded and revised; we could no longer manufacture food supplements containing Vitamins A and D at levels in excess of 10,000 I.U. and 400 I.U. respectively; our customers and their customers in turn, would no longer be able to buy from us food supplements of their choice containing Vitamins A and D beyond the levels of 10,000 I.U. and 400 I.U. although they have been purchasing such products in the past without such restriction, in some instances as long as twenty-five years and even longer.

In addition to this effect on the products we sell,

there will be an immediate disruption of our production planning and manufacturing schedules. This sudden changeover will require new manufacture and new labeling of revised formulations after October 1, 1973. I would estimate that we will have to expend over $75,000 almost immediately, to change labels, formulae, catalogs, etc. On the basis of twenty-five years selling millions of bottles which contain over 10,000 I.U. Vitamin A or 400 I.U. Vitamin D throughout the United States, we can reasonably conclude that our products are safe. Why then should we be prohibited from manufacturing and selling such products and why should we be forced to incur the disruption and expenditure required by the Vitamin A and D regulations which would be effective October 1, 1973?

I respectfully request that this Court grant plaintiff's motion herein for a preliminary injunction to preserve the status quo and prevent the irreparable injury we, as well as others in the industry, would suffer pending the presentation and consideration of plaintiffs' evidence which will demonstrate that the restrictions being imposed are medically and scientifically unreasonable and unsound.

PHILIP POLLACK

Sworn to before me this
13th day of August, 1973.

ROSE E. FOOSE
NOTARY PUBLIC OF NEW JERSEY
MY COMMISSION EXPIRES APR. 3, 1978

AFFIDAVIT OF HAROLD ROSENBERG
(Filed August 15, 1973)

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,

Plaintiffs,

-against-

CASPER W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

Index No.
73 Civ. 3448

AFFIDAVIT

STATE OF NEW YORK)
) SS.:
COUNTY OF NEW YORK)

HAROLD ROSENBERG, D.O., being duly sworn, deposes and says:

I am an osteopathic physician licensed to practice medicine in the State of New York, and am a member of the New York State and New York City Osteopathic Societies.

I am immediate past president of the International Academy of Preventive Medicine. The members of the Academy include physicians, dentists and Ph.D's in the fields of medicine and science, and its members include such leaders in science and nutrition as Dr. Linus Pauling and Dr. Roger Williams. I am also a lifetime member of the New York Academy of Science and a staff member of the Leroy Hospital.

I am a graduate of Drake University where I received my B.A. in biological sciences. In 1951 I graduated the

Philadelphia College of Osteopathic Medicine and thereafter served my internship at the Swedish Hospital in Brooklyn, New York.

Preventive medicine and nutrition have been an intregal part of my work for over twenty years in private practice. In this time I have frequently had occasion to recommend to patients a substantial increase in their daily intake of vitamins and minerals. This includes the intake of levels of Vitamins A and D far beyond the 10,000 I.U. and 400 I.U. which the Food and Drug Administration seeks to fix as the maximum level available on a non-prescription basis. In all my years I have yet to encounter a single case of vitamin toxicity or symptomology of hypervitaminosis, be it Vitamin A or D or any other vitamin, among patients who have taken vitamins at levels far above the limitations which the FDA seeks to establish. Yet after October 1, 1973 I am told that any patient to whom I recommend Vitamin A at a level above 10,000 I.U. or Vitamin D at a level above 400 I.U. (even if it were just one I.U. more) will need a prescription which will have to be filled by a pharmacist.

The medical and scientific literature does not support such a general regulatory restriction on the availability of Vitamins A and D. These substances are essentially food substances. They are not dangerous per se. They are an essential part of human nutrition and differ from alien substances used for medication. Those studies on animals and man which report signs of Vitamin A or D toxicity, frequently deal with animals, infants and young children rather than adults. Even more frequently, and especially with adults, they involve levels

of hundreds of thousands and even millions of International Units of Vitamin A or D over extended periods of months or years before any signs of toxicity are noted.

It is my opinion, shared by many of my colleagues, that the FDA regulations requiring a prescription for any level of Vitamin A or D in excess of 10,000 I.U. or 400 I.U. is unreasonable and unnecessary and totally out of line with the tremendously high levels at which any signs of toxicity have been reported. If these low levels which FDA seeks to fix to non-prescription availability were sound, then innumerable food items, such as liver, sweet potatoes, and others would have to be limited to prescription use. It seems incredible that such food substances be limited to sale by prescription when we have many "over-the-counter" drug items, such as aspirin, which have well-documented histories of danger and abuse, available every day without prescription. I do not suggest that such drugs must necessarily be put on a prescription only limitation, but I do believe that such a limitation for more than 10,000 I.U. of Vitamin A or 400 I.U. of Vitamin D is most inappropriate and unjustifiable.

HAROLD ROSENBERG

Sworn to before me this

11 day of August, 1973.

JACOB LAUER
NOTARY PUBLIC, State of New York
No. 31-[illegible]
Qualified in New York County
Commission Expires [illegible]

UNITED STATES DISTRICT COURT (Filed August 15, 1973)
SOUTHERN DISTRICT OF NEW YORK

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,

Plaintiffs,

-against-

CASPER W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

Index No. 73 Civ. 3448

AFFIDAVIT

STATE OF NEW YORK)
) SS.:
COUNTY OF NEW YORK)

CARLTON FREDERICKS, being duly sworn, deposes and says:

I am a nutritionist and nutrition educator. I received my Ph.D. in Public Health Education from New York University. I have lectured, taught and studied in the field of nutrition since 1937. For many years I had a nationally syndicated radio program on nutrition and I still do many broadcasts in this field.

I have taught nutrition in the Continuing Education Divisions of Brooklyn College, City College and Rockland Community College, and was an adjunct professor in the Continuing Education Division of the New York Institute of Technology. At New York University I taught a course in applied nutrition for health supervisors and I was a member of the post-graduate faculty in nutrition of the Tenth District Dental Society of

which renders them susceptible to toxic effects from Vitamin D at very low doses, it omits the evidence that there is a group of infants whose requirement for Vitamin D is raised to 100,000 units daily. Supplementation to offset this metabolic error must be in massive dosage, or florid rickets will develop. As much as the individual metabolic differences of the latter group should not be used to justify a ceiling of 100000 units of Vitamin D in consumer supplements for daily use, so should the metabolic aberration of the first group not be used to justify restrictions on the availability of genuinely protective amounts of Vitamin D for the average infant, child, and adult. Indeed, osteoporosis in the housebound geriatric population has recently been cited as grounds for more generous use of Vitamin D supplements for the aged who are denied exposure to sunshine.

The most innocuous substance can exhibit toxicity at some level of intake.

Massive doses of everyday foods and condiments would from some subjects prove toxic. Salt, substituted for sugar in infant formulas, has killed numerous babies. Nutmeg in modest dosage has caused hallucination in human beings. Overdoses of milk have been reported to cause calcification of the soft tissues in at least one human being. Large amounts of polyunsaturated fat, administered intravenously to an infant, have resulted in death. A puzzling sickness of an English patient was traced to overdoses of Worcestershire sauce, a condiment used without harm for many decades, by millions of consumers.

If the FDA definition of unsafe dosage of Vitamin A has merit, innumerable common food items consumed by the public should be put on a prescription-only basis. Carrot juice has been reported in large doses to cause carotemia - yellowing of the skin; but its content of Vitamin A, nearly 20,000 units per 8-ounce glass, has been innocuous, despite consumption of the juice, fresh squeezed or canned, by millions of Americans. Those who are fond of carrots, cooked or raw, may easily exceed FDA postulated toxic levels of Vitamin A intake. A modest portion of liver, eaten with spinach and a sweet potato, may yield nearly 80,000 units of Vitamin A.

It should also be noted that rather than there being a "danger" of excess intake of vitamins, the converse is the case. The Schaeffer study introduced at the FDA vitamin hearings from 1968 to 1970, demonstrated the existence of varied population groups whose dietary intakes were below those of the Recommended Dietary Allowance including Vitamin A for which the RDA is only 5,000 I.U. Older people who do not eat the "right" foods and who utilize the foods they do eat less efficiently, need more, not less, supplementation. Medically suggested diets based on the concept that animal fats and cholesterol are responsible for cardiovascular disease avoid the use of whole milk, even for infants, and reduce the intake of butter, liver, organ meats, and fats from meats and other animal proteins. These are measures which do not augment, but decrease the intake of Vitamin A. Recent studies of the U.S.D.A. report a <u>drop</u> in Vitamin A intake in the last two decades.

Dr. Linus Pauling has estimated that the range of require-

ment for Vitamin A in human beings may go from 5,000 units daily to 25,000. It is evident that the F.D.A. proposal to limit Vitamin A potencies to 10,000 units heavily penalizes those whose metabolism does not coincide with that of the mythical "standard reference American".

Vitamin A supplementation is not an invention of the modern vitamin industry. The history of the use of supplements of Vitamins A and D, beginning with codliver oil, is at least a century old. It is not a history of episodes of toxic reactions, but one of benefit to the public. What happens to animals given massive doses of these vitamins, or what has happened to human beings astronomically overdosed with these factors should not be permitted to deprive the great majority of Americans of Vitamin A and D supplements of effective potency. The non-prescription limits of 10,000 I.U. of Vitamin A and 400 I.U. of Vitamin D which the F.D.A. now proposes to fix by regulation are unreasonable and not supported by scientific fact.

S/
CARLTON FREDERICKS

Sworn to before me this

10th day of August, 1973.

ROBERT ULLMAN
Notary Public, State of New York
No. 30-4051200
Qualified in Nassau County
Commission Expires March 30, 1975

AFFIDAVIT OF ROBERT ULLMAN AND EXHIBITS A THROUGH N
ANNEXED THERETO
(Filed August 15, 1973)

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,

Plaintiffs,

-against-

CASPER W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

Index No. 73 Civ. 3448

AFFIDAVIT

STATE OF NEW YORK)
) SS.:
COUNTY OF NEW YORK)

ROBERT ULLMAN, being duly sworn, deposes and says:

I am a member of the firm of Rees & Ullman, attorneys for plaintiffs in this action, and submit this affidavit in connection with plaintiffs' motion for a preliminary injunction herein.

The instant motion by plaintiffs seeks an order, pending a determination of the issues raised by plaintiffs' complaint for a declaratory judgment and permanent injunction, staying enforcement by the Food and Drug Administration (FDA) of new regulations which would require the sale of Vitamin A at levels above 10,000 International Units (I.U.) and Vitamin D at levels above 400 I.U. to be on a prescription only basis.

Annexed hereto as Exhibit "A" is a copy of pages 20723-20725 of the Federal Register of Thursday, August 2, 1973

> "[E]xcessive amounts of vitamin D (of the order of 1,000 to 3,000 iu/kg/day) are potentially dangerous to children and adults and may lead to hypercalcemia and attendant complications....There is no evidence that intakes of the order of 2,000 to 3,000 iu/day produce hypercalcemia beyond infancy."

Annexed hereto as Exhibit "E" is a statement in the Congressional Record of June 7, 1973 (Pg. E3847-3849) by Dr. Linus Pauling, two-time Nobel Prize winner, criticizing the prescription limitations which FDA seeks to impose upon the use of Vitamins A and D. Dr. Pauling states that the optimum daily intake of Vitamin A for many people is 25,000 I.U. and that there is no convincing scientific evidence to support the new regulation. He also observes that FDA's limitations could be extended to ordinary portions of common foods containing amounts of Vitamin A far above 10,000 I.U. Dr. Pauling is a Professor of Chemistry at Stanford University and was Chairman of the Division of Chemistry and Chemical Engineering at the California Institute of Technology. His credentials are set forth at length at page E3848 of the Congressional Record.

Annexed hereto as Exhibit "F" is a statement dated August 8, 1973 of Dr. E. Charaskin, M.D., D.M.D. Dr. Charaskin is an Assistant Professor in the Department of Medicine at the University of Alabama Medical Center and Professor and Chairman of the Department of Oral Medicine. His work in clinical nutrition, and appointment, memberships, publications and honors are set forth in the curriculum vitae annexed to his statement. Considering the FDA's new regulations on Vitamins A and D, Dr. Charaskin states:

"On the basis of my personal experience and my knowledge of the literature, I find it difficult to justify the recent pronouncements by the Food and Drug Administration regarding the dosages of vitamins A and D acceptable for over the counter use."

Annexed hereto as Exhibit "G" is a statement dated August 7, 1972 of Harvey Ross, M.D., Los Angeles, California, expressing his disagreement with the FDA restrictions on Vitamins A and D based on his experience and medical knowledge. Dr. Ross was Vice President of the Gracia Square Hospital Medical Board in New York and is a member of the Board of Governors of the International College of Applied Nutrition. His curriculum vitae is annexed to his statement.

Annexed hereto as Exhibit "H" is a statement dated August 7, 1973 from Dr. J. P. Hutchins, M.D., President of the International College of Applied Nutrition, who states that in his 20 years of medical practice he has not encountered any case of toxic effects among his patients who have taken Vitamin A in excess of 10,000 I.U. per dosage and Vitamin D in excess of 400 I.U. per dosage daily. Dr. Hutchins further states that the prescription limitations fixed by the FDA for Vitamins A and D are unreasonable and without any valid purpose.

The National Clearing House for Poison Control Centers, United States Department of Health, Education and Welfare, Public Health Service, Food and Drug Administration has issued a Bulletin dated April-June, 1972 on the subject matter of "Vitamin Ingestions." Considering the question of Vitamin A intoxication or hypervitaminosis A, the Bulletin states, at page 4 thereof, "Hypervitaminosis A has, with one exception, been associated with intake of

more than 100,000 I.U. a day." Similarly, with respect to Vitamin D, this Bulletin states, at pages 4 and 5, "from an acute single ingestion standpoint, Vitamin D is non-toxic" and that "ingestion of Vitamin D in doses of 100,000 units or more daily in adults or 4,000 units or more daily in children has resulted in hypervitaminosis D." A copy of the Bulletin is annexed hereto as Exhibit "I".

Between 1968 and 1970, the FDA conducted public hearings with respect to regulations dealing with the label statements for dietary supplements of vitamins and minerals and the creation of a standard of identity for vitamin-mineral supplements. The transcript of these two-year public hearings alone consumed over 32,000 pages. The regulations covered by these hearings were actually first proposed in 1962 and were not finalized until August 2, 1973. The final order promulgating these regulations is now the subject of a petition for review before the Court of Appeals. At no time from 1962 through the public hearings, which ended in 1970, and up to December 14, 1972, was any suggestion ever made that the non-prescription use of Vitamins A and D be limited to levels not to exceed 10,000 U.U. and 400 I.U. respectively. Although the public hearings did not deal with any such question of establishing prescription limitations, FDA's own witnesses at these hearings gave testimony as to the exceedingly high levels at which there have been reports of toxic symptoms in the use of Vitamins A and D.

Annexed as Exhibit "J" is a copy of page 2361 of the aforesaid public hearings wherein Dr. Arthur Grollman, M.D. agreed with the statement in his own text that there was little,

if any, evidence of Vitamin D toxicity and that the only cases of Vitamin A toxicity with which he was familiar involved doses of 100,000 I.U. per day over an extended period of time. The relevent pages of Dr. Grollman's text were also received in evidence and copies thereof are attached to the transcript page of his testimony. Dr. Grollman testified as a pharmacologist and as Professor of Experimental Medicine at the University of Texas, Southwestern Medical School.

Annexed hereto as Exhibit "K" is a copy of pages 14,572 and 14,573 of the transcript of the aforesaid hearings wherein FDA witness, Dr. Victor Herbert, M.D., testified that Vitamin A toxicity could occur with amounts in excess of 100,000 units per day. Dr. Herbert testified as an expert in nutrition and as a Professor of Medicine at the Mt. Sinai School of Medicine, New York, New York.

Annexed hereto as Exhibit "L" is a copy of page 23,230 wherein Dr. Harold E. Harrison, M.D. testified that the level at which manifestations of Vitamin A toxicity occurs would be in the neighborhood of 100,000 I.U. per day over several months. Dr. Harrison testified for the FDA in his capacity as Pediatrician in Chief of the Department of Pediatrics, Baltimore City Hospital and Professor of Pediatrics at Johns Hopkins University School of Medicine. He was also a committee member of the Recommended Daily Allowances Committee of the Food and Nutrition Board.

Annexed hereto as Exhibit "M" is a copy of pages 14,766 to 14,770 of the aforesaid transcript wherein FDA witness Professor Olaf Mickelsen, Ph.D. testified that toxicity with

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chase, the words prescribed by this paragraph shall immediately and conspicuously precede or follow such name, except:

(i) Where the characterizing flavor and a trademark or brand are presented together, other written, printed, or graphic matter that is a part of or is associated with the trademark or brand may intervene if the required words are in such relationship with the trademark or brand as to be clearly related to the characterizing flavor; and

(ii) If the finished product contains more than one flavor subject to the requirements of this paragraph, the statements required by this paragraph need appear only once in each statement of characterizing flavors present in such food, e.g., "artificially flavored vanilla and strawberry."

PART 3—STATEMENTS OF GENERAL POLICY OR INTERPRETATION

§ 3.10 [Revoked]

2. The provisions of § 3.10 are hereby revoked.

§ 3.23(b) [Revoked]

3. The provisions of § 3.23(b) are hereby revoked.

§ 3.201 [Revoked]

4. The provisions of § 3.201 are hereby revoked.

Effective date. Labeling may be changed to comply with this regulation beginning August 2, 1973. All labeling ordered on or after December 31, 1973, and all labeling used for products shipped in interstate commerce on or after December 31, 1974, shall comply with this regulation; provided, that the label of a flavor need not conform to paragraph (g) (2) of this regulation prior to December 31, 1974, if it bears a statement certifying that the ingredients are listed as being generally recognized as safe on a reliable published industry association list.

(Secs. 403, 701(a), 52 Stat. 1047, 1055; 21 U.S.C. 343, 371(a))

Dated: July 25, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.73-15700 Filed 8-1-73;8:45 am]

PART 3—STATEMENTS OF GENERAL POLICY OR INTERPRETATION

Status of Vitamin A and Vitamin D

In the FEDERAL REGISTER of December 14, 1972 (37 FR 26618) the Commissioner of Food and Drugs proposed that preparations containing vitamin A in excess of 10,000 international units (IU) per dosage unit and preparations containing vitamin D in excess of 400 IU per dosage unit shall be dispensed on prescription. A correction, which did not alter the intent of the proposal, was published in the FEDERAL REGISTER of January 4, 1973 (38 FR 799). Sixty days were allowed for comment.

Approximately [illegible] and 1,000 signatures on [illegible] received in response to the proposal were received from a wide segment of the public, including individual consumers, physicians, nurses, pharmacists, dietitians, home economists, nutritionists, nine pharmaceutical manufacturers, a number of vitamin preparation distributors, and health food store operators. Comments from the medical profession were presented by the American Academy of Pediatrics and the American Medical Association. Organized consumer groups that responded were the National Health Federation, Oregon Student Public Interest Research Group, Committee Against Health Fraud, Inc., Committee for the Cessation of "Fortification" of Food Products with Calciferol Hormones, Virginia Citizens Consumer Council, Inc., Consumers Cooperative of Berkeley, Inc. Comments were also submitted by the Wisconsin Alumni Research Foundation, The Ann Arbor Dietetic Association, the American Dietetic Association, and five trade associations: The Pharmaceutical Manufacturers Association, East Coast Health Food Corporation, the National Food, Drug and Cosmetic Association of Manufacturers and Distributors, Inc., the National Nutritional Foods Association and the National Association of Pharmaceutical Manufacturers.

GENERAL COMMENTS

The proposal was controversial and generated widely ranging comments regarding broad issues raised by the use of vitamins in foods and drugs. Many of these comments are not appropriate for consideration of the more limited issues raised in the proposed regulation regarding vitamin A and vitamin D. With respect to the broad issues of vitamin and mineral use the Commissioner notes that several regulations including comprehensive discussion of these issues have been published in the FEDERAL REGISTERS of January 19 and March 14, 1973 (38 FR 2124, 6950) and elsewhere in this issue of the FEDERAL REGISTER.

The majority of responses from individual consumers were opposed to the proposal. In reviewing such comments, the Commissioner is concerned that the public is not fully aware of the provisions and medical basis of the proposal. For example, the tenor of many comments was that vitamin A and vitamin D would be available only on prescription. Form letters and several petitions, which were submitted with a number of signatures, contained key statements, presumably the basis on which the signatures were obtained, that bear very little, if any, resemblance to the actual provisions of the proposal. It is clear that the majority of individual consumers responding had been improperly or inadequately informed.

The comments fall into three general categories:

(1) Those who agree that the action proposed by the Food and Drug Administration is necessary and that the prescription levels proposed for vitamin A and vitamin D are suitable. Those who agreed included the American Academy of Pediatrics, the American [illegible] Association, five consumer groups, [illegible] physicians, dietitians, nutritionists, home economists and other professionals in the scientific and health care community, and a few individual consumers.

(2) Those who agree that such vitamins can be toxic, but only at levels higher than those levels proposed by the Food and Drug Administration. The majority of the drug manufacturers and trade associations, and some consumers, made responses that were in this category.

(3) Those who disagree with the proposal entirely, stating that such vitamins are foods and that individuals should have the right to ingest any amount desired. The comments from most individual consumers, operators of health food establishments and a consumer group, were in this category.

SPECIFIC COMMENTS

1. A number of comments contended that "natural" vitamins (including vitamin A and vitamin D) and minerals are foods rather than drugs and should not be treated as drugs. Some viewed "natural" vitamins as safe whereas synthesized vitamins may be (or are) toxic.

The question regarding whether a vitamin is a food or drug generated considerable discussion. The tentative and final orders promulgating §§ 80.1, 125.1, and 125.3 (21 CFR 80.1, 125.1 and 125.3), published in the January 19, 1973 FEDERAL REGISTER (38 FR 2143, 2152) and elsewhere in this issue of the FEDERAL REGISTER discuss this matter in detail. The Commissioner concludes, on the basis of all the available evidence, that vitamins between the upper and lower limits as specified in § 80.1 are adequate for all known nutritional needs for normal individuals and that nutrients at these levels are dietary supplements which are foods for special dietary use. No evidence was submitted in the comments to establish a food or nutritional use of vitamin A or vitamin D at higher levels, except for a limited number of persons with poor vitamin D absorption who need up to 1000 IU of this vitamin for nutritional purposes under medical supervision. With that one exception, which is recognized in the revised regulation, intake of vitamins at levels exceeding the upper limits as specified in § 80.1 are therefore appropriate only for therapeutic purposes and thus are properly classed as drugs.

This position is entirely consistent with the Food and Drug Administration's long-standing interpretation and application of the act. See, e.g., Kordel v. United States, 335 U.S. 345 (1948), in which the Supreme Court upheld the conviction of an individual for marketing "health food products" consisting of "various vitamins, minerals, and herbs" on the ground that they were misbranded drugs. See also United States v. 3 Cartons * * * "No. 26 Formula GM etc.," 132 F. Supp. 569 (S.D. Calif. 1952).

Alleged differences in vitamins based on their source is also discussed in the

tentative and final orders promulgating §§ 80.1 and 125.1–125.3. There is no scientific evidence to suggest that there is a difference in the metabolic actions or toxic effects of synthetically produced vitamins as compared with those from natural sources.

2. Several manufacturers and trade associations objected to the proposal on the ground that the proper classification of OTC drug levels of vitamins would be made in the near future by the appropriate OTC drug advisory review panel and that levels established now by the Food and Drug Administration would only be on interim measure. These comments expressed the opinion that deferring action on this proposal would not result in any significant hazard to the public health.

In the preamble of the proposal the Commissioner stated his reasons for separating vitamin A and vitamin D from the other vitamins at this time and establishing levels above which these vitamins are limited to prescription distribution. The continuing information available to the Commissioner regarding the toxicity of vitamin A and vitamin D and the continuing reports of promotion of large amounts of these vitamins for a variety of purposes makes this action necessary at this time in the public interest.

3. A number of comments from individual consumers and those representing the vitamin industry agreed that vitamin A and vitamin D are toxic in amounts in excess of known requirements, but stated that such levels are much higher than the limitations proposed. Some comments offered a level of 25,000 IU of Vitamin A and 1,000 IU of Vitamin D as providing a sufficient safety margin for known toxicity. Other comments contended that the proposed levels were suitable for children, but higher levels would be more appropriate for adults. A number of comments felt the proposed levels were arbitrary and without scientific merit or support. Several of the comments had made a review and provided their own analysis of the bibliography prepared by the Food and Drug Administration at the time the proposal was published in the FEDERAL REGISTER. Generally, these comments stated that toxicity below 50,000 IU daily for vitamin A was rare and that vitamin D toxicity reports would not support the vitamin D level proposed.

Several other comments recommended lower levels than those proposed. A comment from a physician at a university School of Medicine, Department of Biochemistry, supported the proposal, but stated that 5,000 IU for vitamin A would be a more judicious level. Another comment from the Department of Chemical Pathology, the United Liverpool Hospitals, Liverpool, England, included a reference to a paper written by the respondent regarding self-medication with multivitamin preparations and recommended that 100 IU of vitamin D per dosage unit be the limit for non-prescription marketing.

The Commissioner has carefully reviewed the comments and analysis regarding the [illegible] tion for establishing the proposed vitamin A and vitamin D limits and finds that such comments do not sufficiently support a revision of the proposed limits. No evidence refuted the toxicity findings on which the proposal was based, and further reports of toxicity continue to accumulate. Based on consultation with the most knowledgeable experts available, the Commissioner finds that the scientific consensus is that the proposed limits are appropriate at this time.

The Commissioner of Food and Drugs will soon publish in the FEDERAL REGISTER a request for submission of all data and information relevant to the safety and effectiveness of vitamins and minerals for OTC drug use, pursuant to the procedures established in 21 CFR 130.301, published in the FEDERAL REGISTER on May 11, 1972 (37 FR 9464). The members of the OTC drug review panel for vitamin-mineral drugs are presently being selected. This panel will have full authority to review and re-evaluate the proper dividing line between OTC and prescription levels of vitamin A and vitamin D, and to recommend to the Commissioner any changes in the regulations promulgated by this order, in its report. Thus, the levels of vitamin A and vitamin D for prescription use in this regulation are established on an interim basis only. These regulations will be revoked upon promulgation of a final OTC drug monograph for vitamin-mineral drugs incorporating final prescription levels for these two vitamins.

4. A number of comments, particularly those from individual consumers, state that it is not logical to require a prescription for dosage levels of vitamins that may be lower than the vitamin content of an average serving of certain foods. A few comments expressed concern that normal diets with or without appropriate vitamin supplementation may lead to toxic conditions.

The Commissioner recognizes that many common foods contain a variety of vitamins and minerals in widely ranging amounts, and that some common foods contain vitamin A in excess of 10,000 IU per serving. It is also recognized, however, that these foods particularly rich in vitamin A are rarely consumed daily in sufficient quantity over the long periods of time required to lead to toxic manifestations. The concern of the Food and Drug Administration is the availability of vitamin A and vitamin D in large dosage units in medicinal forms, i.e. capsules and tablets, particularly in view of the multiplicity of other sources of this vitamin in the daily diet. The convenience of ingestion in this form on a routine basis encourages excessive intake of these vitamins far beyond the average amounts ingested in normal diets of conventional food over extended periods of time. Adequate amounts of vitamin A and vitamin D will continue to be available as dietary supplements and are not being removed from the market place. The margins of safety provided in the levels established by this proposal were developed to take into account the wide ra[illegible]es of vitamin [illegible] of vitamin A and [illegible] that are usually implicated in toxic conditions.

5. Comment was received that consumers would be able to ingest as many dosage units as they desired and therefore the proposed limits would have no effect. The Commissioner cannot agree with this concept. Today's consumers are increasingly knowledgeable and are concerned about the health and safety of themselves and their family. The Commissioner believes that most consumers will carefully consider the advisability of taking dosage units in excess of suitable recommended daily dosages. Conscientious consumers will have a basis upon which to make a judgment as to their intake of these vitamins. The fact that a small number of consumers will abuse their health by excessive intakes of drugs, regardless of regulatory and other approaches to curtail such abuse, is no reason to forego a reasonable regulation that will afford appropriate public health protection for the vast majority of the public.

6. The Committee on Nutrition, American Academy of Pediatrics, and several other respondents commented on the special needs for vitamin D in foods for special dietary use in specific medical conditions. Foods designed to provide sound nutrition to individuals with poor vitamin D absorption require higher than normal levels of vitamin D. Such individuals may require dietary intakes up to 1000 IU as part of their overall dietary management.

The Commissioner recognizes that foods represented solely for use under medical supervision to meet nutritional requirements in specific medical conditions have a place in medical care of a select group of individuals who have diagnosed conditions that will benefit from the use of complete foods containing up to 1000 IU of vitamin D. The marketing of such foods is permitted in compliance with § 125.1(b) being published elsewhere in this issue of the FEDERAL REGISTER. The regulation for vitamin D has been revised to allow this limited use of a higher amount of vitamin D without a prescription.

7. Comments received from the Council on Foods and Nutrition, American Medical Association, endorse the proposal and include reference to the possible relationship between excess vitamin D and hypercholesterolemia, in addition to the classic form of vitamin D toxicity. The Council also commented that the proposal fails to mention that there is no recommended dietary allowance for vitamin D for adults, since their needs are considered to be met by ordinary mixed diets and exposure to sunlight. The Council, along with other respondents, raised a question regarding a controlled "overage" to assure compliance with label declarations of the amounts present.

The Food and Drug Administration recognizes that there is no recommended dietary allowance for vitamin D in adults except during pregnancy and lactation and therefore considers vitamin D as an

optional component of dietary supplements of vitamins and minerals for adults and older children (21 CFR 80.1). The Commissioner notes that within good manufacturing practices reasonable overages are permissible in formulating drugs and these are recognized in the specification ranges used in determining whether or not a product meets its labeled potency.

8. In response to the proposal, the Wisconsin Alumni Research Foundation resubmitted comments directed to a proposal regarding vitamin D published in the FEDERAL REGISTER of August 28, 1965 (30 FR 11140). The previous proposal was more restrictive than the present one and contained several provisions not currently being considered. Of significance in the comment was concern by the Wisconsin Alumni Research Foundation that the requirements as proposed in 1965 would have the effect of decreasing the vitamin D intake by the general public to a level below their nutritional needs.

The Commissioner concludes that such a situation is clearly not possible as a result of the current proposal, which is directed only at the use of vitamin D as a drug. As a result of the vitamin D content of milk and other foods, and the availability of vitamin D in dietary supplements, the national food supply provides ample vitamin D.

9. Several manufacturers commented that the effective date of any final order with respect to vitamin A and vitamin D should be the same uniform effective date established for recent food labeling revisions. Such an effective date would permit interstate shipments of existing high potency products through December 31, 1974. Several comments also requested that those vitamin A and vitamin D preparations already in commercial channels be allowed continued marketing until existing supplies are exhausted.

Because of the known toxicity and continuing reports of toxic conditions resulting from large dosages over a period of time, the Commissioner concludes that protracted continuation of manufacture and marketing of preparations that do not meet the requirements of this order is not justified. However, a reasonable period of time to allow for orderly reformulation and relabeling, where necessary, is in the public interest to assure continued availability of vitamin A and vitamin D preparations. Therefore, this order shall become effective for products labeled beginning October 1, 1973. No recall of existing stocks is deemed necessary.

10. One comment from a manufacturer stated that the proposal conflicts with the limits for vitamin A established by the food labeling regulations published in the January 19, 1973 FEDERAL REGISTER (38 FR 2124). The Commissioner finds no conflict between this drug regulation and the food regulations. Those vitamin A preparations within the ranges specified in § 80.1 are considered foods and must be labeled as dietary supplements. Those preparations containing vitamin A in excess of the upper limit of these ranges, but less than the proposed prescription drug level, are OTC drugs. Those preparations containing in excess of 10,000 IU of vitamin A per dosage unit are prescription drugs.

11. Several comments requested that a public hearing be held to consider the issues and objections. A hearing on these matters is not mandatory under section 701(a) of the act. The Commissioner concludes that a hearing is inappropriate at this time and that any further delay in promulgation of these regulations is not in the public interest. A hearing on this issue will be available before both the advisory drug panel and the Commissioner under the OTC drug review procedures.

Having considered the comments received, the Commissioner concludes that the proposed regulations are in the public interest and should be adopted as set forth below.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502(a), (f), and (j), 503(b), 701(a), 52 Stat. 1050-1052, as amended, 1055; 21 U.S.C. 352(a), (f), and (j), 353(b), 371(a)) and under authority delegated to the Commissioner (21 CFR 2.120), Part 3 is amended by adding thereto the following new sections:

§ 3.94 Vitamin A preparations for oral use as drugs.

(a) Vitamin A is an essential nutrient for humans. It is widely recognized that large amounts of vitamin A can cause adverse effects, some of which are serious. The U.S. Recommended Daily Allowance (U.S. RDA) for vitamin A is 1500 International Units, (IU) for infants, 2500 IU for children under 4 years of age, 5000 IU for adults and children 4 or more years of age, and 8000 IU for pregnant or lactating women.

(b) In view of the toxicity of excessive consumption of vitamin A, the Food and Drug Administration finds that, in order to protect the public health, oral preparations containing vitamin A in excess of 10,000 IU per dosage unit or recommended daily intake are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

(1) The label bears the legend, "Caution: Federal law prohibits dispensing without a prescription"; and

(2) The labeling bears full disclosure information as required by § 1.106(b)(3)(i) of this chapter, and especially appropriate warnings regarding vitamin A toxicity.

(c) Preparations containing 10,000 or less IU of vitamin A per dosage unit will be regarded as misbranded if their recommended daily intake exceeds 10,000 IU.

§ 3.95 Vitamin D preparations for oral use as drugs.

(a) Vitamin D is an essential nutrient for humans. It is widely recognized that vitamin D, when ingested daily in large amounts, is toxic. The U.S. Recommended Daily Allowance (U.S. RDA) for vitamin D is 400 International Units (IU).

(b) In view of the toxicity of the excessive consumption of vitamin D, the Food and Drug Administration finds that, in order to protect the public health, oral preparations containing vitamin D in excess of 400 IU per dosage unit or recommended daily intake are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

(1) The label bears the legend, "Caution: Federal law prohibits dispensing without a prescription"; and

(2) The labeling bears full disclosure information as required by § 1.106(b)(3)(i) of this chapter, and especially appropriate warnings regarding vitamin D toxicity.

(c) Preparations containing 400 or less IU of vitamin D per dosage unit will be regarded as misbranded if their recommended daily intake exceeds 400 IU.

(d) Foods which are represented for use solely under medical supervision to meet nutritional requirements of persons with poor vitamin D absorption may contain vitamin D not in excess of 1000 IU per dosage unit or recommended daily intake.

Effective date. This order shall become effective on October 1, 1973 for products labeled on or after that date.

(Secs. 502(a), (f), and (j), 503(b), 701(a), 52 Stat. 1050-1052; as amended, 1055; 21 U.S.C. 352(a), (f), and (j), 353(b), 371(a))

Dated: July 25, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.73-15703 Filed 8-1-73;8:45 am]

PART 3—STATEMENTS OF GENERAL POLICY OR INTERPRETATION

SUBCHAPTER B—FOOD AND FOOD PRODUCTS

PART 121—FOOD ADDITIVES

Folic Acid, Potassium Iodide and Kelp

In the FEDERAL REGISTER of January 19, 1973, the Commissioner of Food and Drugs published tentative orders revising regulations for food for special dietary uses and establishing a definition and standard of identity for dietary supplements of vitamins and minerals (38 FR 2143, 2152). In the preamble to the tentative order revising the regulations for foods for special dietary uses, the Commissioner stated that other regulations governing the levels of the food additives folic acid and iodine would be revised at a later date to make them consistent with the levels of these nutrients permitted in foods for special dietary uses and in dietary supplements of vitamins and minerals (38 FR 2145).

No exceptions were received objecting to the provisions of the two tentative orders relating to the levels for folic acid and iodine. Elsewhere in this issue of the FEDERAL REGISTER the Commissioner is publishing a final order promulgating those new regulations with the levels for folic acid and iodine unchanged.

...yield times one-half the ...um of the figure 1 and the national factor for the current year, or (2) the farm marketing quota for the immediately preceding marketing year times one-half factor for the current year. The farm marketing quota so computed for any farm for any year shall be increased by the number of pounds by which marketings from the farm during the immediately preceding year were less than the farm marketing quota (after adjustments): *Provided*, That any such increase shall not exceed the amount of the farm marketing quota (including leased pounds) for the immediately preceding marketing year prior to any increase for undermarketings or decrease for overmarketings. The farm marketing quota so computed for each farm for any year shall be reduced by the number of pounds by which marketing from the farm during the immediately preceding year exceeded the farm marketing quota (after adjustments): *Provided*, That if, on account of excess marketings in the preceding year, the farm marketing quota is reduced to zero pounds without reflecting the entire reduction required, the additional reduction required shall be made in subsequent marketing years.

Section 319(e) provides also, that the farm marketing quota for a new farm shall be the number of pounds determined by the county committee with approval of the State committee to be fair and reasonable for the farm on the basis of the past burley tobacco experience of the farm operator; the land, labor, and equipment available for the production of burley tobacco; crop rotation practices, and the soil and other physical factors affecting the production of burley tobacco: *Provided*, That the farm marketing quota for any such new farm shall not exceed 50 percent of the average of the farm marketing quotas for similar farms for which farm marketing quotas are otherwise established: *Provided further*, That the number of pounds allocated to all new farms shall not exceed that portion of the national reserve provided by the Secretary for establishing quotas for new farms.

Section 319(h) provides that effective with the marketing year beginning October 1, 1976, no marketing quota, other than a new farm marketing quota, shall be established for a farm on which no burley tobacco was planted or considered planted in any of the 5 years immediately preceding the year for which farm marketing quotas are being established.

Section 319(i) provides, in part, that if the Secretary, in his discretion, determines it is desirable to encourage additional marketings of any grades of burley tobacco during any marketing year to insure traditional market patterns to meet the normal demands of export and domestic markets, he may authorize the marketing of such grades without the payment of penalty or deduction from subsequent quotas to the extent of 5 percent of the farm marketing quota for the farm on which the tobacco was produced, and such marketings shall be eligible for price support.

The Act (7 U.S.C. 1301(b)) defines the "reserve supply level" as the normal supply plus 5 percent thereof. "Normal supply" is defined as a normal year's domestic consumption and exports, plus 175 percent of a normal year's domestic consumption and 65 percent of a normal year's exports. A "normal year's domestic consumption" is defined as the yearly average quantity produced in the United States and consumed in the United States during the 10 marketing years immediately preceding the marketing year in which such consumption is determined, adjusted for current trends in such consumption. A "normal year's exports" is defined as the yearly average quantity produced in the United States which was exported from the United States during the 10 marketing years immediately preceding the marketing year in which such exports are determined, adjusted for current trends in such exports.

The subjects and issues involved in the proposed determinations with respect to burley tobacco for the 1973–74 marketing year are:

1. The amount of the reserve supply level.
2. The amount of the national marketing quota.
3. The amount of the national reserve.
4. The national factor.
5. Whether the Secretary should implement the provision in section 319(i) to encourage additional marketings of any grades to insure traditional market patterns.

Consideration will be given to data, views, and recommendations pertaining to the proposed determinations, rules and regulations covered by this notice which are submitted in writing to the Director, Tobacco Division, Agricultural Stabilization and Conservation Service, U.S. Department of Agriculture, Washington, D.C. 20250. All written submissions made pursuant to this notice will be made available for public inspection from 8:15 a.m. to 4:45 p.m., Monday through Friday, in Room 3741, South Building, 14th and Independence Avenue, SW., Washington, D.C. All submissions must, in order to be sure of consideration, be postmarked not later than 30 days from the date of publication of this notice in the FEDERAL REGISTER.

Signed at Washington, D.C. on December 7, 1972.

GLENN A. WEIR,
Acting Administrator, Agricultural Stabilization and Conservation Service.

[FR Doc.72-21502 Filed 12-13-72;8:49 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 3]

VITAMIN A AND VITAMIN D

Proposed Statement of Policy

Large doses of vitamin A and/or vitamin D ingested over long periods of time can cause adverse effects, some of which are serious. Vitamins A and D are fat-soluble and excess quantities accumulate in fatty tissue. The acute and chronic toxicity of these vitamins is documented extensively in the medical literature. Vitamin A is available over the counter in dosage levels up to 10 times the recommended daily dietary allowance (RDA) of the Food and Nutrition Board, National Academy of Sciences-National Research Council (FNB-NRC), and vitamin D is available up to 60 times the RDA. The availability without prescription of these vitamins in high dosage levels contributes significantly to their misuse and the occurrence of serious adverse effects.

In view of the toxicity of excessive quantities of these vitamins, it is of concern to the Food and Drug Administration and medical authorities that there is widespread promotion to the laity of excessive quantities of these vitamins for prophylaxis and treatment of a variety of diseases and disorders. In its "Newsletter" of June 1, 1972 (Vol. 23, No. 9), the American Academy of Pediatrics (AAP) comments on the critical dangers of use of high doses of vitamin A that have been recommended in the lay press, on radio, and on television. For example, the layman is being advised that he would profit from taking 25,000 international units (IU) of vitamin A with 2,500 IU of vitamin D, or twice these amounts, daily.

The AAP Committees on Drugs and on Nutrition published a joint committee statement entitled "The Use and Abuse of Vitamin A" in the journal "Pediatrics," Volume 46, Number 4, October 1971, warning physicians regarding vitamin A toxicity. This article states "Despite awareness of the potential dangers of vitamin A toxicity, the incidence of hypervitaminosis A appears to be increasing. Hypervitaminosis A may result through easy availability of high potency vitamin preparations without prescription and by the overzealous parents who frequently administers vitamins under the popular premise, that, if one is good, two are better. The problem may be compounded by the use of bizarre, highly fortified health foods." The AAP Committee on Drugs specifically has urged the Food and Drug Administration to limit the potency of vitamin A preparations available over the counter.

There exists considerable information in the literature regarding these vitamins and their toxicity. A listing of a number of pertinent articles, many of them recent, regarding these vitamins has been placed on file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6–83, 5600 Fishers Lane, Rockville, Md. 20852 for public view.

The highlights regarding toxicity of vitamins A and D and the rationale for limiting over-the-counter availability of these vitamins are as follows:

VITAMIN A

Adverse effects which result from excess intake of vitamin A include anorexia, growth retardation in children, drying and cracking of the skin, hepatosplenomegaly, increase intracranial pressure, alopecia, migratory arthralgia, bone pain,

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hypomenorrhea, irritability, and headache. Doses of 50,000 IU in adults and 20,000 IU in infants on a daily basis over long periods are known to produce toxicity. At present vitamin A is available over the counter in dosage levels as high as 50,000 IU per dosage unit. In recent years, some physicians and laymen have used large doses of vitamin A in the treatment of acne, although such therapy has not been shown to be safe and effective. Vitamin A in excessive dosages is used over long periods of time for this indication. Adverse effects, particularly increased intracranial pressure which may mimic a brain tumor, have been observed in children and young adults who are receiving vitamin A therapy for the treatment of acne. Reports of such effects have been published in the medical literature.

The position of the AAP on the matter is clear, as cited above.

In the United States, the Food and Nutrition Board, NAS/NRC, is the recognized authority for determining vitamin and other nutritional requirements for the human. The recommended daily dietary allowances (RDA) of the Food and Nutrition Board for vitamin A are 1,500 IU for infants; between 2,000 and 3,500 IU for children 1 to 9; between 4,500 and 5,000 IU for older children and adults; 6,000 IU during pregnancy, and 8,000 IU during lactation.

Based on the above considerations, it is the opinion of the Food and Drug Administration and medical experts that preparations containing vitamin A in excess of 10,000 IU per dosage unit shall be dispensed only by prescription and that for any vitamin A preparation intended for distribution as a dietary supplement or as an over-the-counter drug, the recommended daily dosage shall not exceed 10,000 IU vitamin A.

VITAMIN D

There are marked differences in tolerances to Vitamin D in humans when quantities in excess of normal requirements are ingested over prolonged periods. There are significant numbers of individuals who are hyperreactive to excess vitamin D. Generally, the margin of safety between nutritional requirements and toxic levels is small for vitamin D. The margin is particularly small in those individuals who are hyperreactive.

In infants, children and adults, excessive ingestion of vitamin D results in hypervitaminosis D characterized by anorexia, nausea, weakness, weight loss, polyuria, constipation, vague aches, stiffness, generalized vascular, soft tissue and premature epiphyseal calcification, nephrocalcinosis, hypertension, anemia, hypercalcemia, acidosis, irreversible renal failure and death.

Daily ingestion by infants of doses between 1,000 and 2,000 IU has produced hypervitaminosis D, usually manifested as the infantile hypercalcemia syndrome. There is good evidence suggesting that the supravalvular aortic stenosis syndrome with hypercalcemia in infants and children may result from excess intakes of vitamin D by the infant and/or by the mother during pregnancy. This latter syndrome may have a tragic outcome with severe aortic stenosis, mental and physical retardation, elfin facies, renal failure and death.

The recommended daily dietary allowance (RDA) of the Food and Nutrition Board, National Academy of Sciences-National Research Council of vitamin D for all age groups for which the vitamin is required is 400 IU. Although a daily intake of 400 IU of vitamin D is sufficient to prevent vitamin D deficiencies, preparations are available over the counter in dosage levels up to 25,000 IU per dosage unit. Excessive dosages of vitamin D have also been promoted in the lay press as noted above.

Based on the toxicity of vitamin D, the possibility of severe irreversible adverse effects in some instances, and the narrow margin of safety, it is the consensus of medical experts and the Food and Drug Administration that preparations containing vitamin D in excess of 400 IU per dosage unit shall be dispensed only by prescription and that the recommended daily dosage of any vitamin D preparation marketed as a special dietary food or as an over-the-counter drug shall not exceed 400 IU.

Therefore, because of the toxicity of vitamins A and D, their continued promotion in high doses to the lay person, and the continuing reports of adverse effects attributable to excessive intake of these vitamins, the FDA concludes it is in the interest of consumer safety to take the action herein described.

All vitamins are included among the over-the-counter drugs to be reviewed by an OTC Drug Advisory Review Panel, under the procedures established in the FEDERAL REGISTER on May 11, 1972 (37 F.R. 9464). Safety and effectiveness and more general questions related to adequate labeling of vitamin preparations marketed as OTC drugs will be considered by that panel, as well as the differences between foods for special dietary use, OTC drugs, and prescription drugs as they relate to vitamins. The Food and Drug Administration will publish, in the near future, new regulations governing dietary supplements of vitamins and minerals. Until such time as the OTC Drug Advisory Review Panel has completed its review and the new regulations for dietary supplements of vitamins and minerals are in effect, the Food and Drug Administration will not object to the inclusion in vitamin products marketed as foods for special dietary use or as OTC drugs of vitamin D at levels not exceeding 400 IU per dosage unit or 10,000 IU of vitamin A per dosage unit and with the recommended daily dosage not exceeding 400 IU of vitamin D or 10,000 IU of vitamin A.

Accordingly, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502 (a), (f), and (j), 503(b), 701(a), 52 Stat. 1050-1052, as amended, 1055; 21 U.S.C. 352 (a), (f), and (j), 353 (b), 371(a)) and under authority delegated to him (21 CFR 2.120), the Commissioner of Food and Drugs proposes to amend Part 3 by adding the following new sections:

§ 3.— Vitamin A preparations for oral use as drugs.

(a) Vitamin A is clearly known to be an essential nutrient for humans. Large doses of vitamin A can cause adverse effects, some of which are serious. The toxicity of vitamin A is well documented in the medical literature. The recommended daily dietary allowance (RDA) of the Food and Nutrition Board, National Academy of Sciences-National Research Council of vitamin A are: 1,500 international units (IU) for infants; between 2,000 and 3,500 IU for children 1 to 9; between 4,500 and 5,000 IU for adults; 6,000 IU during pregnancy, and 8,000 IU during lactation.

(b) In view of the toxicity from the use of large doses of vitamin A, the Food and Drug Administration finds that, in order to protect the public health, oral preparations containing vitamin A in excess of 10,000 IU per dosage unit are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

(1) The label bears the legend, "Caution: Federal law prohibits dispensing without a prescription"; and

(2) The labeling bears full disclosure information as required by § 1.106(b)(3)(i) of this chapter, and especially appropriate warnings regarding vitamin A toxicity.

(3) The recommended daily dosage of vitamin A does not exceed 10,000 IU.

(c) Vitamin A preparations labeled or dispensed contrary to this statement will be subject to regulatory proceedings as of (60 days after day of final promulgation in the FEDERAL REGISTER).

§ 3.— Vitamin D preparations for oral use as drugs.

(a) The importance of vitamin D in human nutrition is established. It is also widely recognized that vitamin D, when ingested daily in excessive amounts, is toxic. The recommended daily dietary allowance of vitamin D established by the Food and Nutrition Board, National Academy of Sciences-National Research Council for the prevention of vitamin D deficiency for all age and physiological groups for which the vitamin is required is 400 IU from all sources.

(b) In view of the known toxicity and seriousness of the adverse effects that may be caused by excessive consumption of vitamin D, the Food and Drug Administration finds that in order to protect the public health, oral preparations containing vitamin D in excess of 400 IU per dosage unit are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

(1) The label bears the legend, "Caution: Federal law prohibits dispensing without a prescription"; and

(2) The labeling bears full disclosure information as required by § 1.106(b)(3)(i) of this chapter, and especially appro-

priate warnings regarding vitamin D toxicity.

(3) The recommended daily dosage of vitamin D does not exceed 400 IU.

(c) Vitamin D preparations labeled or dispensed contrary to this statement will be subject to regulatory proceedings as of (60 days after day of final promulgation in the FEDERAL REGISTER).

Interested persons may, within 60 days after publication thereof in the FEDERAL REGISTER, file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding these proposals. Comments may be accompanied by a memorandum or brief in support thereof. Comments received will be available for public inspection at the above office during regular business hours, Monday through Friday.

Dated: November 28, 1972.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[FR Doc.72-21379 Filed 12-13-72;8:45 am]

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

Office of Assistant Secretary for Housing Production and Mortgage Credit—Federal Housing Commissioner (Federal Housing Administration)

[24 CFR Part 201]

[Docket No. R-72-22]

PROPERTY IMPROVEMENT AND MOBILE HOME LOANS

Notice of Proposed Rule Making

The Department of Housing and Urban Development is considering amending Part 201 of Title 24 of the Code of Federal Regulations, Subpart B, "Mobile Home Loans". The amendments issued in accordance with section 2(a) of the National Housing Act, 12 U.S.C. 1701, would permit acceptance of a used mobile home in lieu of the minimum required cash downpayment where the bluebook value of the mobile home being offered as a trade-in is qual to or greater than the minimum cash downpayment. This amendment would permit savings to consumers as the sales tax on the new mobile home being purchased in some cases would be reduced by an amount equivalent to the tax on the value of the trade-in. The second amendment would permit insured lenders to accept a financial statement from a mobile home dealer that has been prepared by a licensed public accountant. This change is necessary as the requirement of certification of financial statements has proved to be an undue burden on small businesses which ordinarily do not have their books certified.

All interested persons are invited to submit written comments or suggestions in triplicate with respect to this proposal, on or before January 16, 1973, addressed to the Rules Docket Clerk, Office of the General Counsel, Room 10256, Department of Housing and Urban Development, 451 Seventh Street SW., Washington, DC 20410. All relevant material will be considered before adoption of a final rule. A copy of each communication will be available for public inspection during regular business hours at the above address.

The proposed rule is issued pursuant to section 7(d) of the Department of Housing and Urban Development Act, 42 U.S.C 3535(d).

Part 201 is proposed to be amended as follows:

1. Section 201.535 is amended to read:

§ 201.535 **Borrower's minimum investment.**

The borrower shall make a minimum cash downpayment of at least 5 percent of the first $6,000 of the total cost of the mobile home as shown in the purchase contract (excluding permissible charges and fees provided for in § 201.530(b)) plus 10 percent of any amount in excess of $6,000. A used mobile home with a blue-book value equal to or greater than the required minimum downpayment may be accepted in lieu of a cash downpayment.

2. Section 201.595(b) is amended to read:

§ 201.595 Dealer investigation, approval, and control.

* * * * *

(b) *Financial statement required.* The insured shall obtain a financial statement of the dealer, prepared by a licensed public accountant, not less than once every 12 months. If no loans have been purchased, prior to the date of such financial statement, the insured shall approve the dealer as provided in paragraph (a) of this section.

* * * * *

Issued at Washington, D.C., December 8, 1972.

EUGENE A. GULLEDGE,
Assistant Secretary for Housing Production and Mortgage Credit—Federal Housing Commissioner.

[FR Doc.72-21523 Filed 12-13-72;8:51 am]

DEPARTMENT OF TRANSPORTATION

Coast Guard

[46 CFR Part 10]

[CGD 72-132PH]

UNINSPECTED TOWING VESSELS

Licensing of Operators; Extension of Time for Comments

In the August 11, 1972, issue of the FEDERAL REGISTER (37 F.R. 16374), the Coast Guard proposed regulations governing the issuance of licenses for the operation of uninspected towing vessels to implement the Towing Vessel Operator Licensing Act, Public Law 92-339, 86 Stat. 427, as amended, 46 U.S.C. 405(b) (July 7, 1972).

Public hearings on the proposed regulations were held in Seattle, Wash.; New York, N.Y.; New Orleans, La.; and St. Louis, Mo. In addition, interested persons were given until October 17, 1972, to submit comments. The Coast Guard subsequently received requests for extension of this period to allow interested individuals and organizations to fully document comments submitted. These requests were considered justified and extensions were granted until November 30, 1972.

Among the comments received during the last extension, several addressed themselves to the question of terminology on the license issued, i.e., whether to call the person an Operator or Second Class Operator as proposed or whether a different title such as the more traditional Master or Mate should be used.

Since these recently received comments on this subject, if adopted, could be considered a substantive change to the regulations as proposed, the Coast Guard feels that an additional extension is warranted. This will allow the public to fully participate in the rule making process and give all interested parties an opportunity to express their views on this issue.

In view of the above, the Coast Guard hereby extends the period for such comments to January 15, 1973. All relative comments received by that time will be considered.

Interested persons may participate in this proposed rule making by submitting written data, views, or arguments to the Executive Secretary, Marine Safety Council (GCM/82), Room 8234, 400 Seventh Street SW., Washington, DC 20590, phone: 202—426-1477. Written comments should include the docket number (CGD 72-132PH), the name and address of the person submitting the comments, and the section of the proposal to which each comment is directed. Copies of comments received will be available for examination in Room 8234, 400 Seventh Street SW., Washington, DC.

Dated: December 8, 1972.

W. F. REA, III,
Rear Admiral, U.S. Coast Guard, Chief, Office of Merchant Marine Safety.

[FR Doc.72-21519 Filed 12-13-72;8:50 am]

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IN THE MATTER OF

PROPOSED STATEMENT OF POLICY
CONCERNING VITAMIN A AND VITAMIN D

OBJECTIONS & COMMENTS OF THE NATIONAL NUTRITIONAL FOODS ASSOCIATION

TO: Dr. Charles C. Edwards,
Commissioner of Food & Drugs
Department of Health, Education
& Welfare
Food & Drug Administration

Sir:

The following comments are respectfully submitted on behalf of the National Nutritional Foods Association with respect to the Proposed Statement of Policy converning Vitamin A and Vitamin D published in the Federal Register on December 14, 1972 (21 CFR Part 3).

The National Nutritional Foods Association is composed of business concerns, located throughout the United States, engaged in the manufacture, distribution and sale of vitamins and dietary supplements. These business concerns include manufacturers, wholesalers and retailers all of whom have a vital interest in the limitations set forth in the Commissioner's Proposed Statement of Policy. These comments are submitted on behalf of the Association and the consumers whose freedom

of choice in the selection of these Vitamins would be unduly and unjustifiably restricted by the implementation of the proposals herein considered.

By the instant proposal, the Commissioner would add two new sections to Part 3 of Title 21 of the Code of Federal Regulations. The first of these sections would declare that any vitamin preparation containing in excess of 10,000 I.U. of Vitamin A is a drug restricted to prescription sale. The second section similarly would declare that any vitamin product containing in excess of 400 I.U. of Vitamin D is a drug restricted to prescription sale. It is respectfully submitted that these limitations are without scientific foundation, are beyond the intent of the provisions of the Federal Food, Drug and Cosmetic Act and constitute an unwarranted interference with the right of the consumer to obtain these ingredients without the burden and expense of prescription limitation.

It is essential to first determine what it is that is here being considered. We are not discussing any matter of drugs of chemicals, but rather common food ingredients. The substances here considered are constituents of common food items such as liver, carrots, spinach and the like as to which there has never been any question of danger or toxicity.

The purported reason behind the present proposal to require prescriptions for Vitamin A in excess of 10,000 I.U. and Vitamin D in excess of 400 I.U. is that there is a danger of toxicity in the inges-

tion of these vitaimins in amounts exceeding those levels. It is asserted, in the Proposed Statement of Policy, that this "danger" of toxicity is well documented in the medical literature. An evaluation of the medical comments and the 9 page listing of this so called literature filed with the Hearing Clerk demonstrates, however, a total lack of support for the arbitrary limitations being proposed herein.

The June 1, 1972 Newsletter comment of the American Academy of Pediatrics (A.A.P.) referred to by the Commissioner (p. 26618 of the Federal Register) is the first example of the inapplicability of these medical references to the present proposal. This comment insofar as it refers to toxic effect, does so solely in terms of infants and children. Moreover, the article specifically purports to be a response to the press, radio and television recommendations of nutritionist Adelle Davis. The A.A.P. comment cites an article written by Miss Davis. That article does not, however, make recommendations directed towards infants and children. Miss Davis' article is clearly in the context of adults. It refers to airplane pilots, automobile drivers and specifically uses herself and the term "adults" in stating her views and recommendations. We submit this A.A.P. comment on toxic effects in infants and children cannot in any way be considered as substantive support for the instant proposal which would require adults desiring to obtain a Vitamin A supplement of anything over 10,000 I.U. to get a prescription.

The nine page bibliography amply demonstrates that there is no basis for prohibiting the sale of Vitamin A and D without prescription at the levels above 10,000 I.U. and 400 I.U. Of the 70 references pertaining to Vitamin A (pages 1 through 6) of the bibliography 53 are dated 1967 and before. Of the 38 references pertaining to Vitamin D, (pages 7 through 9 of the bibliography) 31 are also dated 1967 and before. Thus 84 of the 104 references relied upon to support the danger of toxicity which is the purported basis for the proposed limitations were published before the Food and Nutrition of the National Research Council, National Academy of Sciences published its Recommended Dietary Allowances, Seventh Edition, 1968. At the time when the overwhelming majority of the reports in the Vitamin A bibliography were available, the Food and Nutrition Board stated at page 23 of its publication, "If large doses of Vitamin A (20 to 30 times RDA) or of carotene are ingested for long periods of time, manifestations of toxicity develop." The RDA referred to is of course 5,000 I.U. per day. Thus, the Food and Nutrition Board speaks of manifestations of Vitamin A toxicity at levels of 100,000 to 150,000 I.U. ingested for long periods of time. Considering infants, for whom the RDA is 1,500 I.U. per day, the Food and Nutrition Board noted that the level for toxic resultsis at daily levels of 18,000 units for one to three months.

Considering Vitamin D toxicity, the same Food and Nutrition Board reported at pages 25 and 26 of its 1968 publication that generally "potentially dangerous" levels of Vitamin D were at levels " of the

order of 1,000 to 3,000 I.U./Kg/day" and that "there is no evidence that intakes of the order of 2,000 to 3,000 I.U./day produce hypercalcimia beyond infancy."

It is thus obvious that notwithstanding the reports set forth in the bibliography used to support the present proposal, the Food and Nutrition Board has considered the problem of toxicity at levels far beyond the arbitrary and unreasonable low levels for which prescription requirements are now being suggested. This is the same Food and Nutrition Board, NAS/NRC which the Commissioner has stated in his notice of the instant proposal to be "the recognized authority for determining vitamin and other nutritional requirements for the human" (pg. 26619 Federal Register, Dec. 14, 1972). Moreover, the Commissioner has described the Food and Nutrition Board's 1968 RDA publication as a "source of authentic and reliable information on which to base recommended daily allowances of nutrients (Proposed Finding of Fact No. 9 in Tentative Order concerning 21 CFR Part 125, Special Dietary Use). Surely then, the Food and Nutrition Board's 1968 publication is a recognized authority and source of authentic and reliable information concerning the levels at which there may be a question of Vitamin A and D toxicity.

A review of a substantial portion of the individual reports listed in the bibliography filed with the Hearing Clerk, establishes that the levels of Vitamin A and D wherein a question of hypervitaminosis may arise are far beyond the 10,000 I.U. and 400 I.U. restrictions now being considered. Most of these reports were available when the

Food and Nutrition Board made its findings on the subject, and those articles which appeared afterwards add nothing to the information available to the Board when it published its findings and conclusions.

Considering the articles on Vitamin A teratogenicity we find generally that they deal with animal studies. One study (No. 10, page 1 1960) dealt only with hypovitaminosis instead of the hypervitaminosis which is the subject of the proposed statement of policy. The reports of Warnaky, Wilson, Cohlan and Seward (Nos. 1,3,6, and 17 pages 1 & 2, 1940, 1949, 1953 and 1966) dealt with rats. The Wilson report again was a Vitamin A deficiency study. The two reports by Kalter (Nos. 11 & 12 page 1 - 1960 & 1964) the report by Ferm (No. 14, page 1 - 1965) and the report by Murakami (No. 15, page 2 - 1965) involved studies on mice. Dogs (beagle bitches) receiving daily doses of 50,000 - 125,000 I.U. of Vitamin A were the subject of the Wiersig report (No. 18 page 2 - 1967). Hamsters treated with 75,000 to 400,000 USP units of Vitamin A per Kg body weight and guinea pigs treated with 200,000 units per Kg were reported by Robins (No. 21, page 2 - 1970). Robins reported that these levels were up to several hundred times the minimum daily requirement of each species. Considering the teratogenic effect of these exceedingly high doses of Vitamin A, Giroud (No. 7, page 1 - 1968) noted this action differs with different species, rats and mice being much more sensative than guinea pigs and rabbits. Giroud noted "Vitamin A does not seem to be teratogenic in humans." The most recent report cited

in the bibliography by Shenefelt, 1972 (No. 10, page 2) again observes that these animal studies involve dosages which are hundreds of times the daily requirements.

One of the few human studies in the Vitamin A teratogenicity bibliography involved a daily dosage of 150,000 units of Vitamin A administered to 10 adults for 30 days (Pinkus, No. 1, pg. 1 - 1964). This is at a level 30 times the RDA. Nowhere in the bibliography under Vitamin A teratogenicity do we find any support for restricting the sale of Vitamin A without prescription to 10,000 I.U. The following table demonstrates that an analysis of the Vitamin A toxicity bibliography leads to the same conclusion - the reports concern massive doses of Vitamin A of a magnitude nowhere near the 10,000 I.U. limitation being proposed:

ANALYSIS OF LEVELS OF VITAMIN A TOXICITY REPORT IN FDA BIBLIOGRAPHY

Reference No. and Author	Year	Age of Subject	Vitamin A Dosage	Time Period
(1) Josephs	1944	Infant (34 Mos)	240,000/day	31 mos.
(2) Toomey	1947	Infant (2 yrs)	6,200,000	14 days
(6) Wyatt	1950	3 years	400,000-500,000/day	2 years
(8) Sulzberger	1951	44 years	600,000/day (supplemented by occasional doses of 1,000,000 to 2,000,000 units per day)	18 mos.
(10) Bair	1951	1 yr 4 mos	240,000/day	3 mos.

Reference No. and Author	Year	Age of Subject	Vitamin A Dosage	Time Period
(12) Goldzier	1952	2 yrs.	(5,000/day	2 mos.
			(7,500/day	4 mos.
		(History of	(12,500/day	11 mos.
		one patient)	(150,000/day	4 mos.
			(300,000/day	2 mos.
(13) Bifulco	1953	52 yrs.	100,000/day	4 yrs.
(14) Shaw	1953	25 yrs.	200,000-275,000/day	2 mos.
(16) Gerber	1954	Adult	500,000/day	8 yrs.
(Reports of other authors)		4 Adults	200,000	single dose
		?	50,000-100,000/day	2 yrs.
		?	150,000/day	2 mos.
(17) Tudor	1955	20 mos.	200,000/day	8 mos.
(18) Pickup	1956	6 yrs.	450,000/day	6 wks.
		4 yrs.	325,000/day	2 yrs.
(19) Elliott	1956	21 yrs.	150,000/day	7 mos.
(20) Oliver	1958	14 yrs.*	200,000/day	10 mos.
		Also review of other reports of Vitamin A intoxication (27 infants, 3 children & 6 adults) at levels up to 600,000/day and dose duration to 8 1/2 yrs., ranging from 20 to 400 times the RDA except for one 1955 report of 50,000/day for 3 yrs. by 51 yr. old man.		
(21) Oliver	1958	14 yrs.*	200,000/day	10 mos.
(22) Morrice	1960	14 yrs.*	200,000/day	10 mos.
		15 yrs.	200,000/day	?
		16 yrs.	90,000/day	3 1/2 yrs.
(24) Stimson	1961	32 yrs.	100,000/day	5 yrs.
(Reports of other authors)		54 yrs.	50,000/day	3 yrs
		44 yrs.	1,000,000/day	two occassions 14 and 25 days respectively

*/ Same 14 year old subject.

Reference No. and Author	Year	Age of Subject	Vitamin A Dosage	Time Period
(26) Pease	1962	Infants (7 cases - but no Vit. A determination made in one)	Dosage and time unspecified but conclusion that "the statement that 200,000 units of Vitamin A may be given to a child each day with impugnity appears to be erroneous."	
(27) Sober-Beckara	1963	39 yrs.	75,000-150,000/day 375,000/day for...	8 yrs. then 5 mos.
(30) Bergen	1965	62 yrs.	41,000/day(?)	8 yrs.
(32) Silverman	1965	6 Adults (33 to 80 yrs)	600,000/day	5 wks.
(33) Turtz	1960	17 yrs.	200,000/day	18 mos.
(35) DiBenedetto	1967	51 yrs.	600,000/day	3 yrs.
(36) Muenter	1971	18 yrs. 52 yrs.	100,000-200,000/day 200,000-300,000/day	18 mos. 8 yrs.
(37) Feldman	(1970)	20 yrs. 20 yrs.	100,000-500,000/day 100,000/day	4 yrs. 3 1/2 yrs.
(38) Fedotin	(1970)	18 yrs.	150,000/day	4 yrs.
(39) Nater	1970	11 Adult Fishermen	2,000,000-30,000,000 (20-300 gms halibut liver)	Single dose
(40) Rubin	1970	6 yrs.	400,000-625,000	4 1/2 yrs.
(41) Morrice	1971	Letter to editor which merely refers to reports by Oliver & Morrice which are already listed at Nos. 21 and 22 above.		
(42) Gelpke	1971	15 yrs.	200,000/day	2 yrs.
(43) Weiland	1971	16 yrs.	105,000-305,000/day	6 mos.
(44) American Academy of Pediatrics	1971	Contains footnote references most of which are to a number of the studies reviewed in this table		

The foregoing analysis shows that the bibliography filed with the Hearing Clerk fails to support the drastic and unwarranted require-

ment that Vitamin A in excess of 10,000 I.U. be available only on prescription. Even at the high levels used in these reports, the symptoms which followed were generally found to disappear when such use was discontinued. The reports in this bibliography, including those of recent vintage, overwhelmingly deal with instances of daily intakes of millions or hundreds of thousands of units of Vitamin A over prolonged periods of time. In the one study where there is a report of a case as low as 41,000 units (No. 30, Bergen - 1965) the author noted that the patient's neurotic state may have interfered with her ability to relate her actual daily intake which the author implies may have been higher. Dr. Fedotin in the April 27, 1970 issue of the Journal of the American Medical Association (No. 37 in the bibliography) states that the smallest dose of Vitamin A reported to produce symptoms in an adult is 50,000 units given over an 18 month period. As indicated in the above table, the reports at the 50,000 level are few and far between those of the massive doses which make up the bibliography of Vitamin A toxicity reports. Signigicantly, all the reports concerning 50,000 units predate the Food and Nutrition Board's conclusion that manifestations of toxicity develop at 20 to 30 times the RDA.

The Vitamin D bibliography furnished in support of the 400 I.U. limitation is likewise lacking of persuavsiveness in support of the arbitrary limitation sought to be imposed. As heretofore noted, most of this literature was available before the Food and Nutrition Board's statement in 1968 fixing toxicity levels far beyond 400 I.U. In the Barnes report of 1957 (No. 5 in the Vitamin D bibliography) a 67 year old

patient took 300,000 I.U./day for 3 months or more. Barnes also reported that the shortest time reported for Vitamin D toxicity was 12 days at 750,000 I.U./day. The Hass report (No. 7 - 1958) involved a rabbit study where the authors reported that the minimal conditions for the production of calcinosis were a duration of eight days and a total of 3,000,000 units given in three equal doses at intervals of two days.

In the DeWind report (No. 12 - 1961) a 3 year old boy was given 100,000 units/day plus 2 tablespoons of cod liver oil and multivitamin drops, for 8 months. Taylor (No. 19 - 1966) reported a 41 year old man receiving 200,000 units by injection three times weekly for three weeks. Stickler's report of "Possible Detrimental Effect..." (No. 25 - 1971) told of twins who received up to 800,000 I.U./daily. But this report also stated "There were no episodes of clinically recognized Vitamin D intoxication." The West study (No. 26 - 1971) noted that 25,000 to 75,000 I.U. daily is a range which rarely results in intoxication.

Not only do the reports in this bibliography indicate that toxicity occurs at levels many times the RDA of Vitamins A & D, but several reports demonstrate a lack of toxicity at high dosage levels. Josephs (No. 1 Vitamin A bibliography), for example, cited the observation of an eight month old infant who received 500,000 units of Vitamin A daily over a period of over four months with no symptoms of toxicity and with a normal blood vitamin A level. The 52 year old woman reported by Meunter et al. (No. 36) showed no signs of toxicity when she took 100,000 I.U. Vitamin A daily for three months. Gerber (No. 16) reported two patients

who took 25,000 to 50,000 units of Vitamin A for six years and had no complaints referable to possible vitamin A toxicity. Krause reported the case of a 79 year old man who had taken 50,000 I.U. of Vitamin A, because he thought it was good for him, without any signs or symptoms of Vitamin A toxicity. (No. 6 - Amer. J. of Clinical Nutrition, June, 1965). Krause stated:

> "From a nutritional point of view, it is interesting that the ingestion of this excessive amount of vitamin A for seventeen years did not produce any well recognized signs and symptoms of toxicity."

Standard medical texts likewise demonstrate the absence of any reasonable relationships between the proposed prescription levels of Vitamins A and D and the intake levels which result in the toxic syndrome known as hypervitaminosis. Goodman and Gilman in their leading text, The Pharmacological Basis of Therapeutics, (4th Ed., 1970) note at page 1674 that the reported cases of hypervitaminosis A in children have been associated with the chronic ingestions of from 50,000 to 500,000 units per day (the RDA for infants and children is from 1,500 to 3,500 units per day). Concerning Vitamin D, Goodman and Gilman state at page 1684:

> "There is wide individual variation in the amount of Vitamin D that causes hypervitaminosis. As a rough approximation, it may be stated that the continued ingestion of 150,000 units or more daily by a person with normal vitamin D sensitivity may result in poisoning."

Similarly, the Merck Index (12th Ed., 1972) makes the following observa-

tions as to hypervitaminosis A:

> "Acute toxicity in children has resulted from large doses (several hundred thousand U.S.P. units)... Arctic explorers, on ingesting several million Units of Vitamin A in polar bear or seal liver, have developed drowsiness, irritability, headache, and vomiting a few hours later, with subsequent peeling of the skin.
> Chronic poisoning in older children and adults develops, usually, after doses of 100,000 U.S.P. u./day for many months. It has been shown that infants may develop evidence of toxicity in a few weeks with a dosage of 20,000 to 60,000 u./day of water-dispersible vitamin A."

The same recent edition of the Merck index gives the following information as to hypervitominosis D:

> "Vitamin D 40,000 U.S.P. u./day produces toxicity within one to four months in infants: toxic effects have been observed in adults receiving 100,000 u./day for several mo."

The introductory comments to the proposed statement of policy contains several remarks as to overzealous use of Vitamin A by parents and [illegible] use of "bizarre highly fortified health foods." We respectfully submit that the mere fact that some people fail to follow the directions for daily use that appear on every vitamin product is not a basis for imposing prescription requirements on non-toxic levels of an ordinary vitamin. If this approach were followed to its natural conclusion, then we should put all OTC products on prescription. The simple 5 grain aspirin product is a drug whose actions are not fully understood; it is a product every bit as prone to the "popular premise" referred to in the Statement of Policy "that if one is good, two are better." Yet

aspirin is not a prescription item. Nor are we suggesting that it should be. But by the same token, it is not too much to suggest that simple vitamin products should be accorded the same treatment. To the extent that a question of overzealous use may exist as to infants and children, proper cautionary statements may be appropriate. Indeed, the regulations concerning dietary supplements for infants have been implemented without any question as to the levels of Vitamins A and D fixed thereon. We submit, however, that there is no need or basis to prohibit adults from exercising their freedom of choice in the foods and supplements that they eat without having to go to a doctor to get a prescription. The presecription requirement for Vitamin A above 10,000 I.U. is not supported by the reports and studies in the medical literature. Vitamin A deficient diets are not uncommon in this country. To require a physician's presecription for ordinary dietary supplements, imposes high costs and expenses upon the consumer without just cause.

The natural extension of the instant proposal would be to place prohibitions upon the ordinary foods we eat and require prescriptions for carrots, milk, liver and other common foods. Thus, the United States Department of Agriculture in its Handbook No. 8, "Composition of Foods" shows that ordinary foods contain large amounts of Vitamin A as follows:

Food	Units per 100 gms (3.3 oz.)
Raw Carrots	11,000 I.U.
Raw Beef Liver	43,900 I.U.
Pumpkin Pie	2,400 I.U.
Raw Sweet Potatoes	8,800 I.U.
Spinach	8,100 I.U.

Following the position of the FDA in the Proposed Statement of Policy to its logical conclusion, the butcher would require a prescrip-

tion for the sale of his liver, the vegetable man would require a prescription to sell his carrots and the baker would require a prescription to sell his pumpkin pies. Such a conclusion is obviously irrational and is not a fulfillment of the Congressional direction under the Statute.

The National Nutritional Foods Association is very much concerned about the reference to the health food industry in the Proposed Statement of Policy. It has been shown herein that the medical literature fails to support the imposition of prescription limitations at levels anywhere near those being suggested. Are we then to conclude that the instant proposal is but an oblique attack by FDA on the industry and the millions of consumers who desire to exercise their freedom of choice in selecting the foods they eat by purchasing food at a local health food center. The subject of dosage levels of dietary supplements has been a matter of serious controversy in considering FDA's extensive efforts to change its regulations on foods for special dietary use and impose standards of identity for vitamin supplements. The awesome spector of toxicity as to Vitamin A and D casts an unwarranted cloud over the consideration of these ingredients in the dietary supplement regulations. The present proposal for prescription requirements for Vitamins A and D obviously limits the consideration of objections to the restrictions on these ingredients in the proposed regulations concerning vitamins and dietary supplements just recently announced by FDA. Analysis of the bibliography concerning Vitamins A and D makes clear that no question of

harm or safety exists as to these ingredients at levels far beyond those for which a prescription would be required. The instant proposal should, therefore, not be allowed to interfere with a full consideration of all ingredients effected by the pending dietary supplement regulations.

Finally, we respectfully submit that the instant proposal is beyond the legal authority of the Commissioner in that it is not within the intent of the applicable provisions of the Food and Drug Act. The Vitamins effected by the instant proposal are recognized as safe at levels many times those of the RDA. The U.S. Pharmocopia, recognized as an official compendium of drugs by the Food and Drug Act, lists 25,000 as the usual therapeutic dose of Vitamin A and 25,500-200,000 as the usual dose range. No suggestions are made that a prescription be required at even those levels, let alone any lower levels. It is not the intent of the statute that ordinary food items be converted into prescription drugs simply because some people may exceed the recommended daily dosage thereof. Clearly these ingredients are safe for use without the supervision of physicians at levels far above those presently proposed. To the same effect we could consider salt or even water as dangerous in high levels. Yet no one has ever suggested that these foods be considered prescription items. Clearly the food substances here under consideration do not fall within the provisions of Section 503(b) of the Statute.

The sale of vitamins and food supplements has been governed by regulations in effect since 1941. There is no need now to suddenly remove from the market place vitamins and food supplements which have been

available to the American consumer for over 30 years subject to these regulations. No emergency or iminent threat of danger has been shown to exist to justify the economic hardships which would be imposed upon manufacturers, distributors, retailers and the consumer alike by the sudden and arbitrary prohibitions suggested in the proposed Statement of Policy. The prohibitions are unnecessary, unjust, arbitrary and beyond the purpose and intent of the law.

Conclusion

The Proposed Statement of Policy requiring a doctor's prescription for oral preparations containing Vitamin A in excess of 10,000 I.U. per dosage unit and Vitamin D in excess of 400 I.U. per dosage unit is manifestly unsound, arbitrary and unreasonable. The very medical literature relied upon by the Food and Drug Administration demonstrates that there is no question of safety or harm in daily intakes of these ingredients, at levels many times the restrictive and arbitrary limitations now being proposed. The present law and regulations provide ample means for furnishing relevant information concerning vitamins and food supplements without imposing unnecessary, unreasonable and illegal prohibitions upon the consumer's freedom of choice in the selection of the foods he eats.

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FAT-SOLUBLE VITAMINS

VITAMIN A AND CAROTENE

Vitamin A in the human diet derives from preformed vitamin A and from provitamin A carotenoids. Of the latter, β-carotene is the most important, having the highest vitamin A activity and being the most plentiful carotene present in many important human foods. Carotenes are active only after being converted into vitamin A during or subsequent to absorption through the intestinal wall. One international unit (IU) of β-carotene (0.6 μg all-*trans* β-carotene) is equivalent to one IU of vitamin A [0.3 μg all-*trans* vitamin A alcohol (retinol) or 0.344 μg all-*trans* vitamin A acetate (retinyl acetate)] in the rat.[1] There is no evidence that these same potency relationships do not apply to humans.[2] However, the availability of carotenes in foods as sources of vitamin A for humans is low and extremely variable. Often, factors of 1/2, 1/3, 1/4, or less are arbitrarily used to compensate for this lower availability of carotenes from different foods.

Food-composition tables should show both the β-carotene and the vitamin A content of foods, but one should be aware that other isomers of carotene and vitamin A occur in foods and that these have less vitamin A potency than do their all-*trans* forms. The predominant forms of carotene and vitamin A in nature have the all-*trans* configuration. However, each of the principal carotenoids (α-, β-, and γ- carotenes and cryptoxanthin) is capable of existing (or being formed during heat processing and cooking) in a number of stereoisomeric forms having widely different potencies. Similarly, the vitamin A stereoisomers with *cis*-configurations are less potent than all-*trans* vitamin A. Development and use of analytical methods for evaluating all the various vitamin A-active compounds in foods are needed.

The functions of vitamin A in the body are not completely understood. Its role in the visual process is established best. A specific vitamin A aldehyde (9-*cis*-retinaldehyde) is essential for the formation of rhodopsin and the normal functioning of the retina. A vitamin A-deficient animal has impaired dark adaptation, and measurement of this defect is a common method for studying vitamin A requirement in humans. Vitamin A also participates in the maintenance of the integrity of the epithelial membranes. Stratified keratinizing epithelium is substituted for normal epithelium in the eyes and paraocular glands and in the respiratory, alimentary, and genito-urinary tracts, for example. The common deficiency symptoms are increased susceptibility to microbial infections, xerophthalmia and other eye disorders, loss of appetite and weight, and sterility. There are indications that vitamin A plays a fundamental role at the cellular level and maintains the integrity of the mucopolysaccharide structure of the cell.[8]

Few experiments have been conducted to determine the minimum daily requirement of human adults, and these have involved few subjects. The most widely accepted value resulted from a study conducted by the Medical Research Council in Great Britain,[2] wherein it was suggested that 1,300 IU/day represented the minimum protective dose, based on changes in scotopic vision. This dose was inadequate to maintain blood vitamin A levels and thus would not have maintained liver stores. Animal studies[4-6] have shown that, in the absence of specific factors influencing vitamin A mobilization or transport, significant deposition of vitamin A in the liver does not occur until blood concentrations approach "normal." It was concluded that 2,500 IU of preformed vitamin A per day represented the adult requirement. The FAO/WHO report on vitamin A requirements recommends an intake of 2,500 IU and assumes that the availability of β-carotene is one third and the efficiency of conversion of the available β-carotene is one half. Therefore, on a weight basis, the over-all utilization efficiency of β-carotene is one sixth of that of vitamin A.[7]

However, in most diets, the vitamin A intake is derived both from the preformed vitamin and from carotene with lower availability than that of the preformed vitamin. Therefore, for a mixed diet, the recommended intake of vitamin A should be adjusted upward.

In the United States, the usual foods available are estimated to provide about 7,500 IU of vitamin A per day: about 3,500 IU derived from vegetables and fruits; 2,000 IU from fats, oils, and dairy products; and 2,000 IU from meat, fish, and eggs.[8,9] Thus, about one half of the apparent vitamin A intake is in the form of the provitamin.

For the reference man and woman, the RDA is set at 5,000 IU of vitamin A. For practical purposes, within the United States, it is not considered to be necessary to further adjust the RDA of 5,000 IU for variations in the proportions of preformed vitamin A and provitamin A in the diet.

Since few studies have been conducted on the vitamin A requirement of human infants, the RDA for this age group is deduced from the fact that human milk apparently supplies adequate vitamin A for good health during the first year of life. Human milk has a vitamin A content of 170 IU/100 ml. Assuming consumption of approximately 850 ml of human milk, the infant would receive about 1,500 IU, and this is taken as the RDA.[10]

Investigations are needed to establish the requirements for vitamin A during childhood, adolescence, and other periods when growth spurts normally occur. In their absence, only interpolated estimates of allowances, as shown in the table, can be made for boys and girls of different ages, based on average body weights, plus additional arbitrary amounts to satisfy growth needs.

About 1,000 IU/day additional vitamin A should be provided during the latter two thirds of pregnancy, since the nutritional well-being of the rapidly growing fetus is dependent on the mother's intake of this vitamin. To help ensure the nursing infant ample amounts of vitamin A, an additional 3,000 IU is recommended during lactation.[6,11]

If large doses of vitamin A (20 to 30 times RDA) or of carotene are ingested for long periods of time, manifestations of toxicity develop.[12,13] Carotene in massive doses is not converted to vitamin A rapidly enough to induce vitamin A toxicity, but the excess carotene accumulates in the body without producing clinical symptoms other than yellow skin. This quickly returns to normal when carotene ingestion is stopped. Ingestion of excess vitamin A is more serious. Symptoms of excessive intake include anorexia, hyperirritability, skin lesions, bone decalcification, and increased intracranial pressure. Doses as low as 18,500 IU of a water-dispersed vitamin A–D preparation daily for one to three months are reported to be toxic for infants three to six months of age.[14]

Many factors influence vitamin A requirements. For example, some dietary fat is needed for absorption of vitamin A. Protein malnutrition, however, results both in decreased intestinal absorption and in impairment of blood transport of vitamin A. As with all the fat-soluble vitamins, normal functioning of the gastrointestinal tract, especially bile secretion, is essential for absorption of vitamin A. Laxa-

tives, antibiotics, and certain other drugs decrease the absorption of vitamin A from the intestinal tract, as do various disease states, such as celiac disease and other malabsorption syndromes.

VITAMIN D

Vitamin D is essential at all ages for maintenance of calcium homeostasis and skeletal integrity. Vitamin D can be acquired by ingestion of vitamins D_2 (ergocalciferol) or D_3 (cholecalciferol) and by exposure to certain ultraviolet wavelengths of light, which convert 7-dehydro-cholesterol in the skin to vitamin D_3. Vitamin D deficiency can occur only when the amount supplied by both sources is inadequate. One international unit of vitamin D is 0.025 μg of pure vitamin D_3.

Requirements and Recommended Allowances at Various Ages

The requirement for vitamin D can be met entirely by skin irradiation, so that the need for ingested vitamin D is influenced by the amount of exposure to ultraviolet light. There are few reliable data concerning minimum vitamin D requirements, except for infants. However, long experience has shown that 400 IU/day are sufficient to meet the requirements of practically all healthy individuals, assuming no exposure to ultraviolet light. There is also good evidence that such intakes are nontoxic. The allowances recommended during infancy are well documented [1]; however, those recommended for children and adolescents and during pregnancy and lactation are not well documented and may exceed actual requirements.

In normal full-term infants, intakes of as little as 100 IU/day have prevented rickets.[2-4] Actively rachitic infants have been cured with 300 IU/day.[2] With inadequate vitamin D intake, prematurely born infants develop rachitic lesions more readily than full-term infants, because of their more rapid growth rate. However, the administration of as little as 100 to 200 IU daily has been adequate to prevent biochemical evidence of rickets and to sustain normal skeletal growth in premature infants ingesting adequate amounts of calcium and phosphorus.[4,5] Assuming a satisfactory calcium intake, the ingestion of 400 IU/day provides for excellent skeletal growth, promotes satisfactory

calcium absorption and metabolism, and prevents rickets in practically all normal full-term and premature infants.[1,6,7]

Vitamin D is required throughout the growth period, as evidenced by the rare occurrence of vitamin D-deficiency rickets in adolescents.[8] However, the requirement has been more difficult to determine beyond infancy, because of the greater access to sunlight and various food sources of vitamin D, and because skeletal changes occur less rapidly. In the past, the recommended intake for children and adolescents has been 400 IU/day,[1,9,10] and this is reaffirmed here. Ingestion of this amount of vitamin D protects practically all normal children from deficiency, and there is no evidence that this intake is harmful in any way.[1]

Diet surveys indicate that the majority of adolescents[11,12] do not take vitamin supplements. Because of inconsistency in the addition of vitamin D to commercial foods in North America (in Canada, until very recently, fortification of fluid milk was not permitted), many such individuals ingested much less than 400 IU of vitamin D per day, the total oral intake from all sources amounting to less than 100 IU/day in a number of instances.[13] Despite this, the general health and growth of these individuals were satisfactory. Furthermore, clinical rickets owing to vitamin D deficiency is virtually unknown beyond infancy in North America. These observations should be borne in mind when evaluating the nutritional adequacy of diets of American children and adolescents.

The requirement of vitamin D in adult life is not known. The occurrence of deficiency states (though very rare) indicates that a small need exists,[1] but it is considered that the amounts required are so small that under normal circumstances they are met by the vitamin D content of the usual mixed diet and by exposure to sunlight. For persons working at night, and for nuns and others whose clothing or customs shield them from sunlight, the regular consumption of vitamin D-fortified milk is recommended.

The requirement for vitamin D during pregnancy and lactation also is not known. On the basis of the small amount of evidence,[7] a daily intake of 400 IU is recommended during pregnancy and lactation.

Toxicity

It has long been recognized that excessive amounts of vitamin D (of the order of 1,000 to 3,000 IU/kg/day) are potentially dangerous to children[14] and adults[15] and may lead to hypercalcemia and attendant

complications. It had first been thought that the margin of safety between the vitamin requirement and its toxic dosage was very great. However, relatively recently, circumstantial evidence derived from epidemiologic and metabolic studies of infantile hypercalcemia has tended to implicate vitamin D in the pathogenesis of both the mild and severe forms of this disease.[1,10-19] Vitamin D intakes implicated in hypercalcemia have usually been in the range of 2,000 to 3,000 IU/day, but sometimes the intake has been considerably less than this, and hypersensitivity to vitamin D has been postulated as an additional factor in affected individuals.[1,20] Although the relationship with vitamin D has not been completely proved, and recent estimates[20] place the incidence of infantile hypercalcemia at an extremely low figure, there is a justifiable basis for recommending that vitamin D intakes should not appreciably exceed a total of 400 IU/day during infancy.[1] There is no evidence that intakes of the order of 2,000 to 3,000 IU/day produce hypercalcemia beyond infancy. However, because the long-range effects of small excesses of vitamin D have not been extensively studied in vitamin D-sensitive individuals, the above recommendation for infants is also justified for older children and adults.

Considerations

The decline in the incidence of rickets in the United States in recent decades can largely be credited to the addition of vitamin D to fluid and evaporated milk. Few natural foods contain more than minute amounts of vitamin D. However, in the United States, a number of other foods, such as margarine, milk-flavorings, and certain breakfast cereals, have vitamin D added.[1] In evaluating the total vitamin D intake of the individual in terms of the RDA, the vitamin D content of the milk, of the vitamin supplement, and of all fortified foods must be taken into account. In North America, individuals of all ages consuming an ordinary diet may ingest an appreciable amount of vitamin D without taking a vitamin supplement, and in some individuals the recommended allowance may be considerably exceeded.[1,18] Calculation of individual intakes is often difficult. Vitamin D-addition practices vary from country to country. In the United States, the types of foodstuffs being fortified and the vitamin D concentrations of individual food items are continually being altered by the manufacturers. It is estimated that 85 percent of the fluid milk marketed in the United States has vitamin D added to a concentration of 450 IU/1,000 ml, and almost all brands of evaporated milk and commercial infant formulas

contain this concentration when reconstituted.[1] Thus, within a few weeks of birth, most formula-fed full-term babies will acquire the RDA of vitamin D from the formula, and additional vitamin D is not necessary. Human milk and unfortified cow's milk contain minimal amounts of vitamin D, and, at the present time, fortification of nonfat dry milk is not permitted in the United States. Rickets may occur in breast-fed infants and in those fed unfortified formulas[7]; hence, for these infants a daily vitamin supplement providing 400 IU of vitamin D is recommended. During childhood and adolescence, consumption of vitamin D-fortified milk will usually provide a large proportion of the individual's recommended allowance of vitamin D. Milk consumption tends to be less during adult life, but the vitamin D requirement is also much lower. During pregnancy and lactation, however, many women consume at least one quart of milk per day. If vitamin D-fortified milk is used, the RDA of this nutrient is ingested.

VITAMIN E (α-TOCOPHEROL)

Vitamin E is an essential nutrient in more than twenty vertebrate species, including man. The earliest evidence of deficiency differs with the species, but eventually the hematopoietic, muscular, vascular, and central-nervous systems are affected, as well as the reproductive system in many species of animals, but not in man. The exact biochemical mechanism whereby vitamin E functions in the body is still unknown.

For practical purposes, the tocopherols other than α (e.g., β-, γ-, and δ-), because of their relatively lower potency than the α-form, are disregarded in dietary calculations and evaluations. One international unit of vitamin E is 1 mg of synthetic *dl*-α-tocopherol acetate. The natural form, *d*-α-tocopherol acetate, has a potency of 1.36 IU/mg. The free alcohol, *dl*-α-tocopherol, has 1.1 IU, and *d*-α-tocopherol has 1.49 IU/mg.[1]

In 1949, it was discovered that the normal resistance of red blood cells to rupture by oxidizing agents is markedly reduced in vitamin E deficiency.[2] In vitamin E-depleted monkeys and in some children with kwashiorkor, not only increased hemolysis but also megaloblastic anemia were found, and administration of vitamin E induced a reticulocyte response.[3,4] Studies on the vitamin E requirement of infants established that the amount necessary to prevent hemolysis was within a range of 2 to 10 IU.[5-7] Because of negligible placental transfer, newborn animals, including human infants, have low tissue concen-

trations of vitamin E. Human milk is relatively rich in tocopherol content (2 to 5 IU of α-tocopherol per liter) and would meet the infant's requirement, whereas cows' milk is relatively low (only about 1/10 to 1/2 of the amount in human milk) in vitamin E content and would not be adequate.

In male subjects,[8,9] vitamin E deficiency developed in diets containing 25 percent of calories as fat and supplying about 3 IU of vitamin E daily. As the intake of fat and polyunsaturated fatty acids (PUFA) increased, the requirement for vitamin E increased. The adult needs about 10 IU or less when PUFA intake is low (less than 7 g daily) and about 30 IU when PUFA intake is high (over 35 g/day) and total fat consumption is at the level currently prevalent in the United States (about 40 percent of calories).[8-10]

The increase in vitamin E requirement with increased PUFA intake was also observed in a study of prematures in which a vitamin E-deficiency syndrome developed in those infants receiving formulas relatively high in PUFA content.[11]

Vitamin E requirement apparently is not related to body weight directly nor to calorie intake. It does appear to be related to body weight in kilograms to the three-quarter power ($kg^{0.75}$), sometimes designated as physiologic or metabolic size.[12] (See Appendix 2 for tabulation of body weight, $kg^{0.75}$.) Some support for this relationship is provided by a comparison of vitamin E requirement of 11 species of animals of widely different sizes in which the requirement was found to be related to body weight to the 0.73 power, not significantly different from the commonly used body weight to the 0.75 power.[13] Calculation of recommended allowances as IU = 1.25 × body weight in $kg^{0.75}$ provides the values shown in the table. The calculated allowance for infants, 3 to 6 IU of vitamin E, is in good agreement with the range of 2 to 10 IU established from clinical studies.[5]

The effects of pregnancy or lactation on the requirement for vitamin E have not been established.

Estimates of vitamin E content of diets representative of foods available for daily consumption show wide variation—from about 2 to 66 IU.[10,14] These estimates are made from chemical analyses of individual foods in which there is a wide variation in tocopherol content. The apparent absence of vitamin E deficiency in the general population suggests that the amount of vitamin E in foods is adequate.

Food processing and storage destroy some of the tocopherol content of most foods, and even deep-freeze storage does not completely prevent oxidative destruction of tocopherols. However, ordinary cooking, except deep-fat frying, does not reduce tocopherol content. In the usual

HARVEY M. ROSS, M. D.
9201 SUNSET BOULEVARD · LOS ANGELES 90069
(213) 276-2325

August 7, 1973

Bob Ullman, Esquire
Bass and Ullman
342 Madison Ave
New York, New York 10017

Dear Mr. Ullman:

In referrence to the recent F.D.A. ruling to require prescription for vitamin A above 10,000 units and vitamin D above 400 units, I would like to add my opinion that this ruling has no valid purpose. While it is true that there may be some toxicity from vitamin A and D in large dosages, one must take vitamin A in excess of 100,000 units for a period of time longer than 6 months before toxicity would be expected. I have in my case histories a record of an elderly woman who participated in a study done somewhere which involved taking 300,000 units of A for a long period of time and she was on this dosage for one year before she began to show some side effects of loss of hair. This side effect was quickly reversed when the vitamin was discontinued. In my opinion there is no logical justification for the recent F.D.A. proposal and it seems that this is but a first step towards the total harrassment of all of us who believe in nutrition as a way to maintain and obtain good health.

Very truly yours,

Harvey M. Ross, M.D.

HMR:Tera
Enclosures

HARVEY M. ROSS, M. D.
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HARVEY M. ROSS, M.D.

43	Single Born: Denver, Colorado
Ph.B.	University of Chicago, 1949
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1955-57	U.S.N. Lt. Cdr. Medical Corps Medical Officer, USS Northampton
1957-59	Psychiatric Residency, V.A. Hospital, N.Y.
1960	Psychiatric Residency, New York State Psychiatric Institute
1960-69	Gracie Square Hospital, New York City Staff Physician, Clinical Director, Acting Director, also private practice
1969-72	Private Practice in association with Allan Cott, M.D.

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District Branch of the American Psychiatric Association
New York Academy of Medicine
New York Academy of Science
Pan American Medical Association
Academy for Orthomolecular Psychiatry, Founding Member
International College of Applied Nutrition, Fellow

Research:

Controlled Fasting Treatment for Schizophrenia - in progress with Allan Cott, M.D.

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August 7, 1973

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Editor-in-Chief
HAROLD STONE, D.D.S.

Mr. Robert Ullman
Bass & Ullman
342 Madison Avenue
New York, New York 10017

Dear Mr. Ullman:

In all my 20 years of medical practice, I have not seen or heard of any case of poisoning from Vitamin A or Vitamin D. My patients have taken Vitamin A in excess of 10,000 I.U. per dosage and Vitamin D in excess of 400 I.U. per dosage daily without any toxic effects.

The FDA proposal requiring a doctor's prescription for oral preparations containing Vitamin A in excess of 10,000 I.U. per dosage unit and Vitamin D in excess of 400 I.U. per dosage unit is unreasonable and without any valid purpose.

Sincerely,

J. P. Hutchins, M.D.

J. P. Hutchins, M.D.
President

National Clearinghouse for Poison Control Centers

Bulletin

April-June 1972

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
Public Health Service
Food and Drug Administration
Washington, D.C. 20204

VITAMIN INGESTIONS
BY GEORGE D. ARMSTRONG

Over the past several years, vitamins have been exceeded only by aspirin in the number of ingestions reported to the Clearinghouse. In direct contradiction to other most frequently ingested products such as aspirin, bleaches and pesticides which trended downward, vitamin ingestions as overdoses in children increased from 1.7% in 1965 to 5.1% in 1969. In 1970 and again in 1971, a slight drop to 4.9% and 4.8%, respectively, is probably of little real significance.

Public and medical knowledge of the relative safety of vitamins probably results in a laxity in reporting ingestions. Were this factor eliminated, vitamin ingestions might have trended upward.

Although the percentage of vitamin ingestions dropped slightly, the total number of reported ingestions for children increased to 4053 in 1971. This represents the greatest number of ingestions of any year thus far, and an increase of almost 18% when compared to 1970. (There was a 9% increase of all reports in children under 5). Symptoms were reported in 127 cases and 45 children were hospitalized.

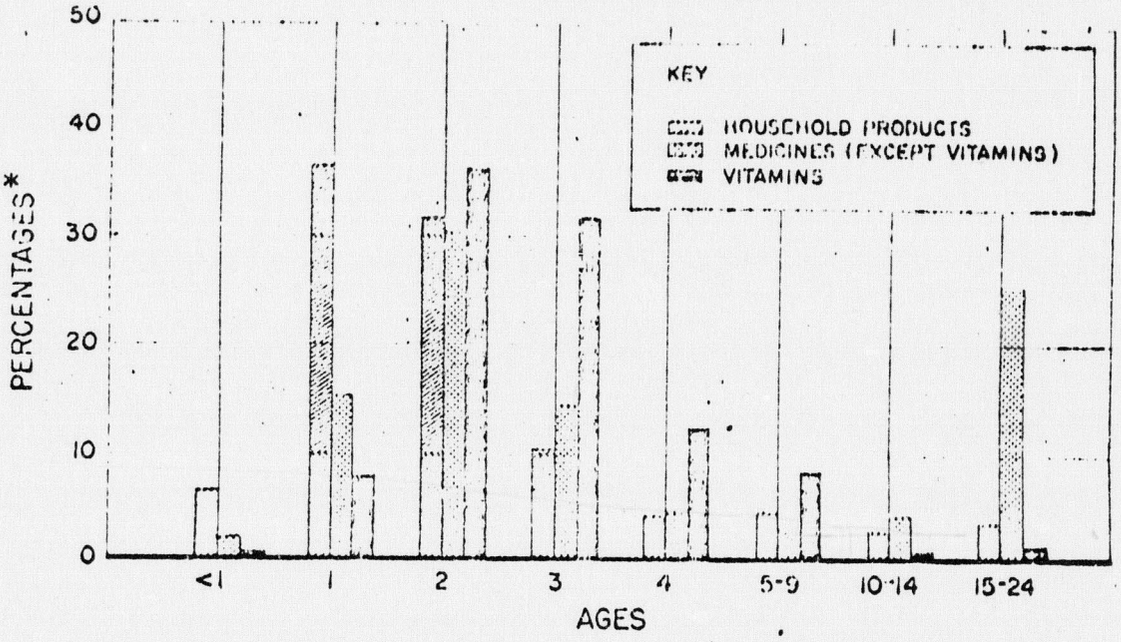
The causes of this constant rise in the number of ingestions are equivocal, at best, but surely some factors that influence the rise are availability, attractiveness, virtual universality of parental "overconcern" for childhood nutrition and increased numbers of total reports received from the Centers.

Vitamin manufacturers have been criticized for their not infrequent commercials depicting vitamins as "tasting good", "being friends", and other slogans which encourage confidence associations by children.

Vitamin poisonings in adults are usually associated with faddism. Ingestion of specific vitamins for "health kicks" and various ailments other than vitamin deficiencies has been surrounded by controversy. The use of vitamin E to prevent sterility, vitamin A to prevent infections, and, most recently,

(2)

COMPARISON OF RELATIVE AGE FREQUENCY OF 1971 INGESTION REPORTS OF VITAMINS, ALL OTHER MEDICINES AND HOUSEHOLD PRODUCTS



* THE PERCENTAGES WERE CALCULATED FROM THE TOTALS OF THE AGE GROUPS SHOWN.

vitamin C for the prevention and/or amelioration of colds has polarized both physicians and laymen alike into believers and non-believers. The object of this article, however, is not to examine these controversies, but to point out the fact that they do exist and that they might influence the number of ingestions reported to the Clearinghouse.

In the 1971 reported cases involving children that were treated, 908 of the 1030 total treated cases had no symptoms. Fifty-eight cases of nausea, vomiting, and/or abdominal pains were reported. Twelve children exhibited lethargy, two rashes, two pneumonias, two elevated temperatures, and one ataxia. Forty-five cases presented with other, unspecified symptoms. The cases reported as hospitalized (45) were not investigated for authenticity. No fatalities were reported. Of particular note is that over fifty percent of ingestions for all ages occurred in two and three year olds. Of the ingestions involving all age groups (4769), 4661 were considered accidental, 48 resulted from attempted self poisoning, and 60 were for unknown reasons. Four of the self poisonings were considered to be suicide attempts and 15 were gestures.

As illustrated by the graph, vitamin overdose is a childhood problem with abrupt decreases in the number of overdoses following the third year. Vitamin overdose follows the pattern

of all other medicines until the early teenage years. During the preteen years, the percentage of ingestions of all medicines rises upward from 0 years old to a peak at 2 years old, down to a plateau at 4 years old where the level remains fairly constant until the early teens. Vitamins follow a pattern that is similar but with certain distinguishing factors. The ascension to the peak at 2 years old is more abrupt but the decline is more gradual and continual without the leveling off that occurs with all other drugs. The third group shown on the graph is household products. As expected, the number of ingestions peaks early (at one year old) and declines as in all medicines to a fairly constant level at four years old.

Graph specifications:
formula -

$$\frac{\text{(number of ingestions of x category at y age)(100)}}{\text{number of ingestions of x category for ages 0-24 years}} = \%$$

for household products, n = 42308; vitamins, n = 4499; all other medicines, n = 53417

Multivitamins

As would be expected, multivitamins represented a large proportion of vitamin statistics. The quantities required to constitute an acute toxic dose of multivitamins are so massive as to virtually eliminate the possibility. Even multivitamins in combination with minerals or fluoride as a single ingestion should be of no more consequence than gastrointestinal irritation with or without purgation. However, chronic ingestion of large amounts could possibly cause hypervitaminoses A and/or D and fluorosis. A more probable cause of hypervitaminoses is the ingestion of therapeutic or high potency multivitamins or in single entity products of Vitamin A or D.

So called therapeutic and high potency vitamins often represent doubling of the standard formulation. From a toxicological standpoint, one needs to distinguish between the accepted meaning and the literal meaning of multivitamins. The general conception of multivitamins is that of a product that contains several B vitamins, vitamins A, C, and D, and possibly a small amount of iron. Literally, the definition of multivitamins is a product that consists of more than one vitamin. Using the literal definition, the potential for toxicity increases tremendously for some products and is essentially eliminated for others. For example, a product consisting of high concentrations of vitamins A and D has a much greater toxic potential than a product consisting entirely of the standard B vitamins (with the inference that the oral route is the method of administration). For the sake of clarity, the accepted definition of multivitamins is used throughout this

article.

Vitamin A

Acute vitamin A poisoning, following a single dose of several hundred thousand units, has been reported in infants. This would represent an extremely large quantity of multivitamins, but only 3 or 4 capsules of certain vitamin A preparations. Symptoms of acute intoxication in infants included increased intracranial pressure with bulging fontanel and vomiting. Discontinuance of the drug alleviated symptoms within three days.

Often studied, but still controversial, are the polar bear liver ingestion incidents. Most investigators agree that the rich vitamin A content of the liver was responsible for the toxic effects. However, agreement has not been reached as to whether toxicity was caused by a single ingestion or by chronic ingestions with acute onset of symptoms. In either case, the symptoms were acute in onset and developed in otherwise apparently healthy individuals within 24 hours postprandially. Symptoms included drowsiness, sluggishness, irritability, irresistable desire to sleep, severe headache, and vomiting, followed by peeling around the mouth within the first 24 hours. Later generalized peeling of the face and/or body occurs.

Interestingly, reports of "sloughing of skin from head to foot" following ingestion of polar bear liver date back to 1596. More recently, experiments involving single ingestions of polar bear liver had both symptomatic and asymptomatic results.

Chronic vitamin A intoxication, hypervitaminosis A, is characterized by disappearing eyebrows, dry rough skin, and cracked lips, followed by severe headache and generalized weakness. Premature closure of the epiphyses and arthralgia are common in children. Decalcification of bone, hemorrhage, and enlargement of the liver and spleen also occur. Hypervitaminosis A has, with one exception, been associated with intake of more than 100,000 units a day. Exactly how vitamin A exerts its toxic effects is not known.

Vitamin D

From an acute single ingestion standpoint, vitamin D is nontoxic. Toxicity problems arise only from large doses for long periods of time. Initially, vitamin D was thought to have a wide margin of safety between the recommended and toxic doses. Recently, however, the margin of safety was found to be much narrower than once thought for chronic use in high doses. The so-called sunshine vitamin, due to the conversion of provitamin to the vitamin in the presence of sunshine or other irradiation, has been incorporated in many foods such as milk and butter to insure adequate amounts in the diet. Ingestion of vitamin D in

doses of 100,000 units or more daily in adults or 4000 units or more daily in children has resulted in hypervitaminosis D. Symptoms simulate hypercalcemia and consist of weakness, fatigue, lassitude, headache, nausea, vomiting, diarrhea, anorexia and pruritus. Impairment of renal function may be manifest as polydipsia, polyuria, nocturia and albuminuria. Metastatic calcification of the kidney and other organs may result in irreversible damage. Treatment consists of immediate withdrawal of the vitamin, a low calcium diet and a generous fluid intake along with acidification of the urine. Cortisol has been used to lower plasma calcium levels to normal.

Other Vitamins

In discussing vitamins other than A and D, the distinctions between side effects, adverse effects, and toxic effects is often evasive. In fact, certain undesirable effects have been reported by some sources as adverse effects and by others as toxic effects. Undesirable effects have been reported from Vitamins C and K and niacin. As vitamin K is rarely found around the home it will not be considered in this article. Vitamin C in megadoses has been reported to cause diarrhea and mild diuresis. In fact, some physicians have used vitamin C in large doses for its laxative effect. According to the AMA Drug Evaluations 1971, "There is no evidence that large doses are harmful". Niacin in large doses for long periods of time has been reported to cause hyperglycemia, jaundice, gastrointestinal irritation, and peptic ulcer. In therapeutic doses, peripheral vasodilation with resultant flushing and pruritus has occurred. Niacinamide, which exhibits the same activity as niacin except for vasodilation, has largely replaced niacin in vitamin preparations. Vitamin E and the other B complex vitamins are essentially non-toxic when given orally.

SUMMARY

Of the vitamins commonly found in the homes, only vitamin A possesses significant single-dose toxicity potential. Therefore, when a physician or poison control center receives a call concerning a vitamin ingestion he should attempt to decipher the ingredients of the preparations with particular note to vitamin A and iron, and their concentrations. If they are not present or are in subtoxic concentrations then giving the child milk should be sufficient placebo to appease the child's parents. If iron intoxication is imminent then the patient should be treated accordingly. Although single ingestion vitamin A poisonings are rare, they have occurred. If potentially toxic amounts have been ingested, treatment should consist of emesis or lavage followed by symptomatic treatment.

Acute symptoms from chronic ingestion of vitamins A and D should be treated as described earlier.

In conclusion, vitamin ingestions as overdoses usually follow a benign, asymptomatic course with unremarkable recovery following discontinuance of the drug. However, the possibility for toxic symptoms, debility and death should not be excluded, especially when high dose chronic intake of vitamins A and/or D are involved.

during the week. Isn't it true, Doctor, that the toxic effects of Vitamin D have been observed in adults receiving 100,000 units per day for several months?

A Yes.

Q Are you acquainted with the Merck Manual, 11th Edition?

A Yes.

Q If it appeared in that manual, would you accept it?

A The Merck Manual I think is probably true.

Q Now, we had children on Vitamin A. Now, as for adults, Hypervitaminosis A, isn't it true, Doctor, that this condition has been described only in patients receiving in excess of 100,000 units a day?

A That would be very plausible.

Q If that statement appeared once again in the Merck Manual, would you accept it?

A As probably correct, yes. Of course, in all of these, Mr. Pendergast, you have to consider the time, the length of time. So that when I say I would consider it, it would depend on how long. If you took, say, 50,000 for two or three years, that might give a worse effect than taking 500,000 for three weeks or a month.

So when I am very vague about this, it is because your questions do not give me amounts and time, duration. All of this must be taken into account. In a particular individual, there will be variations in different individuals, many variables.

tissue, and the lungs and kidney are 40 times as rich as muscle. Inasmuch as this vitamin is so important for growth it is interesting to find it in large quantities in milk and in the yolk of eggs. In fact, milk, eggs and green vegetables are the chief sources of this vitamin for man. Cod-liver oil has long held a position of importance in medicine because it contains large amounts of this vitamin in addition to the antirachitic factor (vitamin D). The livers of other fish than the cod contain much larger quantities of this vitamin than does the liver of that species. For example, the liver of the halibut may contain 100 times as much; in fact 1 per cent by weight of halibut-liver oil may be vitamin A. The cod, like other fish, gets its supply of vitamin indirectly from the algæ upon which the smaller fish and lower forms of marine life feed, and these small fish serving as food for the cod furnish it with the vitamin, which in turn is stored in the fat of the liver.

On account of its solubility in fats, vitamin A is stored in the animal body in larger amounts than are some of the other vitamins, so that no symptoms of deprivation are seen until this store has become exhausted. Young adult rats apparently can store sufficient to keep them alive for about 6 months. Probably 95 per cent of the vitamin is stored in the liver. The accumulation in the liver is lowest at birth and tends to increase with age. Milk, eggs, and other foods contain a mixture of vitamin and carotene, the proportions of each varying often according to species. For example, about two-thirds of the vitamin activity of Guernsey milk is due to carotene while Ayrshire milk owes about one-third of its activity to carotene, and in Jersey milk there are about equal quantities of vitamin and provitamin.

Absorption and Excretion

Vitamin A is absorbed well, reaching its maximum blood level in 3 to 5 hours after administration. The absorption of carotene is more variable and slower, reaching its maximum in 7 to 8 hours. Carotene dissolved in oils or given with a fat diet is utilized well, but when given with a low-fat diet its absorption is less satisfactory. It should not be given with liquid petrolatum as it is soluble in this vehicle and, therefore, will not be absorbed. In the presence of hypothyroidism, also, the body is unable to utilize carotene.

When large amounts of vitamin A are ingested, part is stored in the body while the remainder is destroyed, very little being found in the excreta.

Toxicology

902 Following the ingestion of excessive amounts of the vitamin (100,000 units or more daily for several months) toxic symptoms may ensue. These include anorexia, irritability, pruritus, alopecia, tenderness of the bones, hepatomegaly, and neurological disturbances suggestive of a brain tumor. Ocular changes include papilledema, paralysis of the extra-ocular muscles, diplopia and rarely, exophthalmos. The effects on the bone resemble those induced by parathyroid hormone but, unlike the hormone, vitamin A also affects the cartilage and causes periosteal proliferation of the bones. Acute vitamin A intoxication has occurred in arctic explorers after eating polar bear or bearded seal liver and in infants and children given excessive doses. Rapid recovery follows withdrawal of the vitamin.

oil, such as salmon, sardines, and herring, are rich natural sources of the vitamin. The yolk of eggs is also an excellent source, and it is not destroyed by boiling or by storage. Milk and butter do not contain much vitamin D unless the cows from which they are derived are fed irradiated foodstuffs. Living plant tissues such as leafy vegetables probably contain no vitamin D. Exposure to the sunlight serves as the principal method whereby the organism obtains its requirement for the essential vitamin. Persons who do not expose themselves to light (as among the Moslems who practice Purdah) are for this reason liable to suffer from osteomalacia, the form in which avitaminosis D affects the adult. Even where the diet is deficient in vitamin D, exposure to sunlight, as among the laborers of the Orient, prevents the appearance of the disorder.

Action

Vitamin D facilitates the absorption of calcium from the intestine and is essential for the normal deposition of mineral in the osteoid and cartilaginous matrix of bone. The mechanism of this action and the metabolism of vitamin D in the body are not established. Since vitamin D activates alkaline phosphatase, an enzyme concerned in bone metabolism, it has been suggested that the vitamin is concerned in the action of this enzyme.

Metabolic balance studies in the human indicate that vitamin D stimulates the intestinal absorption of calcium only in cases of rickets but not when given to normal subjects, except occasionally as a late and probably secondary phenomenon. The effects of vitamin D on the serum and urinary calcium are largely independent of each other. The increase in serum calcium is due to withdrawal of calcium from bone; the increase in serum phosphorus results in an elevated urinary excretion of phosphorus. Only in severe cases of refractory rickets does vitamin D in large doses increase tubular reabsorption of phosphorus. Some patients with sarcoidosis are hypersensitive to vitamin D and respond by an elevation in serum calcium. This hypersensitivity is antagonized by cortisone, the administration of which in sarcoidosis results in a decline of the elevated serum calcium to normal.

Toxicology

Excessive amounts of vitamin D lead to a condition of hypervitaminosis. With moderate overdosage there is a fall in the amount of calcium and phosphate in the intestinal contents and an overcalcification at the growing ends of bone. The latter condition is ascribed to the excessive calcium and phosphorus in the blood and the action of the phosphatase or calcifying enzyme. In severe poisoning with this vitamin the calcium and phosphate may be drawn from the bones in spite of the overcalcified epiphyses, and there may be a net loss of mineral salts in the bones. Abnormal deposition of calcium in the blood-vessels and soft tissues has also been described after the administration of excessive doses of certain artificially prepared concentrates containing vitamin D. More recent work indicates that the toxicity observed in earlier work was due to the presence of impurities in irradiated mixtures. There is a wide margin of safety in the use of purified preparations and entire safety in the use of natural preparations.

Therapeutic Use

Exposure to sunlight remains for the adult the chief means for avoiding avitaminosis D. The routine prophylactic administration of some form of vitamin D, as fish oil, viosterol, or calciferol, is advocated for children. Vitamin D is a specific for the cure of rickets and osteomalacia. The use of some vitamin D preparation is also advocated during pregnancy, since the demand for the vitamin is increased by gestation.

The recommended daily allowance of vitamin D is shown in Table 38–1. Premature infants require large doses (4,000 units). For the treatment of rickets and osteomalacia the administration of 1,500 units daily are advocated. In certain cases of "refractory" rickets in which the normal response to vitamin D therapy is not observed, massive doses may be required. However, when using doses greater than 20,000 units daily for infants or 50,000 units for a child, weekly determinations of the blood calcium level should be made since vitamin D in large doses may raise the blood calcium to toxic levels.

The use of dihydrotachysterol, a compound related to vitamin D_2 in hypoparathyroidism, has already been described in Chapter 34.

U.S.P. PREPARATIONS

ACTIVATED 7-DEHYDROCHOLESTEROL. Activated 5,7-Cholestadien-3β-ol, Cholecalciferol, Vitamin D_3, $C_{27}H_{44}O$, occurs as white, odorless crystals. It is insoluble in water. Usual dose: Daily, 10 mcg. (400 U.S.P. Vitamin D Units); in rickets, prophylactic, 10 mcg. (400 Units), and therapeutic, 125 mcg. (5000 Units); in hypocalcemic tetany, up to 5 mg. (200,000 Units).

CALCIFEROL, Ergocalciferol, Vitamin D_2, $C_{28}H_{44}O$, occurs as white, odorless crystals. It is insoluble in water; soluble in alcohol, in chloroform, in ether, and in fatty oils. Usual dose: Daily, 10 mcg. (400 U.S.P. Vitamin D Units); in rickets, prophylactic, 10 mcg. (400 Units), and therapeutic, 125 mcg. (5000 Units); in hypocalcemic tetany, up to 5 mg. (200,000 Units).

CALCIFEROL CAPSULES, as usually available, contain the following amounts of Calciferol: 1.25 mg. (50,000 U.S.P. Vitamin D Units). Category and dose: *See* CALCIFEROL.

CALCIFEROL SOLUTION is a solution of calciferol in an edible vegetable oil or in polysorbate 80 or in propylene glycol. It contains, in each Gm., not less than 0.25 mg. (10,000 U.S.P. Vitamin D Units) of $C_{28}H_{44}O$. Category and dose: *See* CALCIFEROL.

VITAMIN E

Evans and his co-workers found that when rats were fed on synthetic food mixtures with the proper mineral constituents added and vitamins A and B the animals would grow and appear to be perfectly normal, but sooner or later became sterile. The sterility is due to a deficiency in the diet of certain natural foods containing vitamin E, and can be cured by giving these foods or by giving concentrated extracts of the foods. In the male there are changes in the germ cells passing on in severe cases to loss of the seminiferous epithelium, while in the female there is death and reabsorption of the developing embryos. The growth of the embryos seems to be normal for a time, but about the eighth day there is retardation in development, and fetal deaths occur about the twelfth day, although there

BEST COPY AVAILABLE

A Vitamin D, excessive doses of D could be toxic; of K could be toxic.

Q Getting away now from the stipulated population group of infants, what amounts of what agents would be toxic?

A To an adult?

Q Yes. To and adult.

A Amounts in excess of 100,000 units of vitamin A per day could be toxic to an adult and produce nerve damage.

Q Over what period of time?

A That would depend on the body stores the individual started with at the beginning of the period of ingestion of a large dose.

Q Doctor, this 1968 publication of the recommended dietary allowances that you have at your left hand --

EXAMINER MARRIS: P-651.

MR. ULLMAN: Yes, sir.

BY MR. ULLMAN:

Q Is it not a fact that the 1968 RDA publication talks of manifestations of vitamin A toxicity in large doses of 20 to 30 times the RDA's, that is 100,000 to 500,000 units?

A That is why I said over 100,000.

Q Are you personally familiar with any recent reports of vitamin A toxicity in any reputable publication, say the Journal of the American Medical Association?

A There is a report in the American Journal of Medicine

RS-6

on nerve toxicity of vitamin A.

Q What was the toxic amount of vitamin A involved in that report?

A There were several cases reported. The amounts were in excess of 100,000 a day.

Q Are you familiar with the last report of vitamin A toxicity in the Journal of the American Medical Association?

A To which report do you refer?

Q Report in the Journal of the American Medical Association, August 26, 1967.

A Could you show me that reference, please?

EXAMINER HARRIS: Has it been previously identified, Mr. Ullman?

MR. ULLMAN: No, Your Honor. I will be glad to have it marked.

EXAMINER HARRIS: Journal of the American Medical Association, August 26, 1967. O-224-62 -- is it?

MR. ULLMAN: 55, sir.

EXAMINER HARRIS: 55.

(Exhibit No. O-224-55 was marked for identification.)

INDEX

BY MR. ULLMAN:

Q Doctor, do you happen to be familiar with this report?

A I don't recall reading --

EXAMINER HARRIS: Excuse me, Doctor.

iron deficiency anemia in the patients at the Johns Hopkins Comprehensive Child Care Center?

A I believe they fall in the same category.

Q By that, you mean in the same general range, this 33 percent figure?

A The range, yes.

Q Turning to your answer 22, Doctor, you were there discussing supplemental levels, or therapeutic levels of vitamins. In the last sentence of that answer you mention "special toxicity problems with respect to the fat soluble vitamins, especially A and D, when ingested by the infant."

Would I be correct that the chronic toxic dose in the child age group one to three would be in the neighborhood of 100,000 International Units per day over a period of about six months?

A I don't think it would take six months. I think the dosage range is about right. But it would produce toxic manifestations in considerably less than six months.

Q Approximately what period of time?

A Several -- two or three months.

Q But the dosage range of about 100,000 units per day is essentially correct?

A Yes.

Q With respect to vitamin D, are you familiar with the American Academy of Pediatrics' recommendation or finding with

Q What do you mean by "essential"?

A By "essential" we mean the body can not synthesize these amino acids at a rate which will provide maximum growth and maximum health.

Q Does the same hold true as to the fatty acids?

A Linoleic acid has been accepted, plus linolenic acid, as the two that must be provided in the diet, because man and many other animals are unable to synthesize those two fatty acids.

Q Are there others scientists believe are needed in human nutrition?

A Not that I know of.

Q On page 2433, Doctor, you were discussing on lines 19 through 25 the maxima in the RDAs, and you were specific about the possibility of excessive intake of the fat-soluble vitamins. Those are vitamins A and D, are they not, Doctor?

A Primarily, yes.

Q Is it not true that hypervitaminosis A has been found generally in children in amounts of 50,000 to 500,000 units per day?

A In that general area, yes.

Q Do you recall the RDAs?

A Five thousand for Vitamin A, for adults.

Q So that hypervitaminosis condition is in the area of 10 to 100 times higher?

A. Approximately.

Q. Is it not true that hypervitaminosis D has been found to result generally from ingestion of 150,000 units or more a day?

A. In this case of hypercalcemia in children.

In Great Britain there is no valid information which would permit us to say that these children were getting a definite level of Vitamin D in their diet. So that as far as I am aware the implication has been made that in Great Britain the infants with hypercalcemia have gotten considerably lower than -- you said 500,000, was it?

Q. 150,000 units daily.

A. -- 150,000 daily. Yes. The implication has been that they have been getting considerably less than that. But I can not say what they have been getting.

MR. PENDERGAST: I would like to have marked for identification the "Pharmacological Basis of Therapeutics," by Goodman and Gilman.

EXAMINER HARRIS: Has that not been identified?

MR. PENDERGAST: Only various pages.

EXAMINER HARRIS: What pages do you want?

MR. PENDERGAST: Page 1691. I believe the latest edition is the Third Edition.

EXAMINER HARRIS: 0-228-94.

is10

(Exhibit 0-228-94, was marked for identification.)

BY MR. PENDERGAST:

Q Are you acquainted with this text which I just identified?

A Yes, I have used it.

Q Do you find it a reputable text?

A Yes, sir, some parts.

Q Are we going to find a part that is not?

A I am not sure.

Q I show you page 1692, the right-hand column entitled "Hypervitaminosis D," where it says: "As a rough approximation it may be stated that the continued ingestion of 150,000 units or more daily may result in poisoning."

Do you accept that as an accurate statement?

MR. ANDERSON: Objection. No contradiction.

EXAMINER HARRIS: Sustained.

MR. PENDERGAST: All right.

MR. ANDERSON: I wonder, sir, if we could set up a situation where prior to the reading of these comments into the transcript I could get a look at what is being proffered? I hate to leap up and interrupt counsel. But the offer is never made to me. Therefore, we have the material read into the record.

EXAMINER HARRIS: It might save time.

MR. ANDERSON: It might, sir.

EXAMINER HARRIS: I have on occasion had that done.

MR. ANDERSON: Yes, sir.

MR. PENDERGAST: If Mr. Anderson will just tell me what he wants, I will comply.

MR. ANDERSON: It is just that I hate to jump up and interrupt.

EXAMINER HARRIS: The next time you have an excerpt for contradiction purposes show it to Mr. Anderson before you read it.

MR. PENDERGAST: Yes, sir.

MR. KLEINFELD: Is this directed to all counsel?

EXAMINER HARRIS: It might save time.

MR. KLEINFELD: I prefer not to. It is improper. It gives Mr. Anderson a chance to make objections and speeches, and it is not appropriate.

EXAMINER HARRIS: Mr. Anderson is entitled to make objections.

MR. KLEINFELD: At the right time.

EXAMINER HARRIS: It should be before you read the excerpt into the record.

MR. KLEINFELD: Yes, sir. But he knows before I read the excerpt, or anybody reads the excerpts, whether there is a contradiction. I think it is most unfair to give Mr. Anderson the copy before I read something to the witness, or

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show it to him.

EXAMINER HARRIS: I will handle it at the proper time. Let opposing counsel show the excerpts to Mr. Anderson before they are read.

BY MR. PENDERGAST:

Q Is it not true that the possibility of excessive intakes of Vitamins A and D is a possibility only when you reach levels far higher than the RDAs?

A In the case of infants I am not ready to say "Yes" as an answer to this, because the evidence from England -- this which I have seen -- is still not complete enough to permit putting any ceiling below which toxicity did not develop in these children.

Q How about adults?

A Adults are much less susceptible, or appear to be, to toxicity from Vitamins A and D, than infants.

Q Would I be fair then in characterizing your answer to my question to be that for adults the answer is Yes?

A They can take these levels, somewhere in the neighborhood of 100 -- is it 150 that Goodman and Gilman listed? -- 150,000 international units of Vitamin D, over a short period of time, without showing too many sumptoms of toxicity.

Q On page 2445 of the transcript you were asked concerning a product containing egg calcium products. Egg

COMPOSITION OF FOODS, 100 GRAMS, EDIBLE PORTION

Item No.	Food and Description	Vitamin A Value Internat'l Units
11	Amarinth, raw	6,100
37	Apricots: Dehydrated, sulfured, nugget-type & Pieces: uncooked	14,100
39	Apricots: Dried, sulfured: uncooked	10,900
	Meats, poultry, etc; canned	
110	Liver, strained	24,000
111	Liver & Bacon, strained	22,000
	Vegetables, canned:	
118	Carrots	13,000
121	Spinach, creamed	5,000
	Beet greens, common:	
392	Raw	6,100
393	Cooked, boiled, drained	5,100
	Carrots:	
619	Raw	11,000
620	Cooked, boiled, drained	10,500
	Carrots: Canned: Reg. Pack	
621	Solids and liquid	10,000
622	Drained solids	15,000
	Carrots: Special dietary pack (low-sodium)	
624	Solids and liquid	10,000
625	Drained solids	15,000
627	Carrots: Dehydrated	100,000
	Chard, Swiss:	
639	Raw	6,500
640	Cooked, boiled, drained	5,400
	Chicken: Fryers (weight, ready to cook, with giblets, more than 1-3/4 lbs.)	
695	Giblet: Cooked, fried	5,760
758	Chives, raw	5,800

EXHIBIT "N"

Item No.	Food and Description	Vitamin A Value Internat'l Units
	Collards:	
	Raw:	
805	Leaves, without stems	9,300
806	Leaves, including stems	6,500
	Cooked, boiled, drained:	
807	Leaves without stems, cooked in small amount of water	7,800
808	large amount of water	7,800
809	Leaves, including stems, cooked in samll amt. of water	5,400
	Frozen:	
810	Not thawed	6,800
811	Cooked, boiled, drained	6,800
	Cress, garden:	
935	Raw	9,300
	Cooked, boiled, drained,	
936	Cooked in small amt. of water, short time	7,700
937	Cooked in large amt. of water, long time	7,000
	Dandelion greens:	
950	Raw	14,000
951	Cooked, boiled, drained	11,700
	Dock (curly or narrowleaf dock, broadleaf dock, and sheep sorrel):	
953	Raw	12,900
954	Cooked, boiled, drained	10,800
	Eggs:	
	Dried:	
982	Yolk	5,980
	Kale:	
	Raw:	
1153	Leaves, without stems, midribs	10,000
1154	Leaves, including stems	8,900
	Cooked, boiled, drained:	
1155	Leaves, without stems, midribs	8,300
1156	Leaves, including stems	7,400
	Frozen:	
1157	Not thawed	8,200
1158	Cooked, boiled, drained	8,200

Item No.	Food and Description	Vitamin A Value Internat'l Units
	Lambsquarters:	
1239	Raw	11,600
1240	Cooked, boiled, drained	9,700
	Liver:	
	Beef:	
1266	Raw	43,900 */
1267	Cooked, fried	53,400 "
	Calf:	
1268	Raw	22,500 "
1269	Cooked, fried	32,700 "
	Chicken, all classes:	
1270	Raw	12,100 "
1271	Cooked, simmered	12,300 "
	Hog:	
1273	Raw	10,900 "
1274	Cooked, fried	14,900 "
	Lamb:	
1275	Raw	50,500 "
1276	Cooked, broiled	74,500 "
	Turkey, all classes:	
1277	Raw	17,700 "
1278	Cooked, simmered	17,500 "
	Mustard greens:	
1366	Raw	7,000
1367	Cooked, broiled, drained	5,800
	Frozen:	
1368	Not thawed	6,000
1369	Cooked, boiled, drained	6,000
	Mustard spinach: (tendergreen)	
1370	Raw	9,900
1371	Cooked, boiled, drained	8,200
1472	Parsley(common garden (plain) and curled-leaf varieties, raw	8,500
	Peaches:	
	Dehydrated, sulfured, nugget-type and pieces:	
1485	Uncooked	(5,000)

*/ Values vary widely in all kinds of liver, ranging from about 100 I.U. to more than 100,000 I.U. per 100 grams.

Item No.	Food and Description	Vitamin A Value Internat'l Units
	Peas and Carrots, frozen:	
1534	Not thawed	9,300
1535	Cooked, boiled, drained	9,300
	Peppers, hot, chili:	
	Mature, red:	
	Raw:	
1540	Pods, including seeds	21,600
1541	Pods, excluding seeds	21,600
1542	Canned, chili sauce	9,590
	Dried:	
1543	Pods	77,000
1544	Chili Powder with added seasoning	65,000
	Pokeberry (poke) shoots:	
1647	Raw	8,700
	Cooked, boiled, drained	8,700
	Pumpkin:	
1832	Canned	6,400
	Sausage, cold cuts, & luncheon meats:	
1986	Braunschweiger	6,530
	Liverwurst:	
2003	Fresh	6,350
2004	Smoked	6,530
	Spinach:	
2169	Raw	8,100
2170	Cooked, boiled, drained	8,100
	Canned:	
	Regular pack:	
2171	Solids and liquid	5,500
2172	Drained solids	8,000
	Special dietary pack (low-sodium):	
2174	Solids and liquid	5,500
2175	Drained solids	8,000
	Frozen: Chopped:	
2177	Not thawed	7,900
2178	Cooked, boiled, drained	7,900
	Leaf:	
2179	Not thawed	8,100
2180	Cooked, boiled, drained	8,100
	Squash:	
	Butternut:	
2205	Raw	5,700 */
2206	Baked	6,400 "
2207	Boiled, mashed	5,400 "

*/ Value based on freshly harvested squash. The carotenoid content increases during storage, the amount of increase varying according to variety and conditions of storage. More information is needed on the relative contents of the individual carotenoids and their rates of increase under usual storage conditions before a suitable vitamin A value can be derived for the stored product.

Item No.	Food and Description	Vitamin A Value International Units	
	Swamp cabbage:		
2238	Raw	6,300	
2239	Cooked, boiled, drained	5,200	
	Sweet potatoes:		
	Raw:		
2246	All commercial varieties	8,800	
2247	Firm-fleshed */(Jersey types)	9,200	**/
2248	Soft-fleshed " (mainly Puerto Rico variety)	8,700	***/
	Cooked, all:		
2249	Baked in skin	8,100	
2250	Boiled in skin	7,900	
2251	Candied	6,300	
	Canned: Liquid pack, solids and liquid:		
2252	Regular pack in sirup	5,000	
2253	Special dietary pack, without added sugar & salt	5,000	
2254	Vacuum or solid pack	7,800	
	Dehydrated flakes:		
2255	Dry form	47,000	****/
2256	Prepared with water	12,000	

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*/ Term refers to the flesh of the cooked product.

**/ Values for commercial varieties having deep-orange flesh average about 10,000 I.U. per 100 grams; light yellow, about 600 I.U.

***/ Values for commercail varieties range from 8,000 to more than 20,000 I.U. per 100 grams. Porto Rico, the main variety, has a value around 8,000 I.U.

****/ Value varies widely; it is related to variety of sweet-potato. Range in dehydrated form is 21,000 to 72,000 I.U. per 100 grams, and 5,000 to 18,000 I.U. in product prepared for serving.

Item No.	Food and Description	Vitamin A Value Internat'l Units
	Tomato Juice:	
	Dehydrated (crystals):	
2292	Dry form	13,100
	Turnip greens, leaves, including stems:	
2354	Raw	7,600
	Cooked, boiled, drained	
	cooked in -	
2355	small amount of water, short time	6,300
2356	large amount of water, long time	5,700
	Frozen:	
2358	Not thawed	6,900
2359	cooked, boiled, drained	6,900
	Vegetables, mixed (carrots, corn, peas, green snap beans, lima beans), frozen:	
2403	Not thawed	5,000
2408	Vinespinach (basella), raw	8,000

DEFENDANT'S NOTICE OF MOTION TO DISMISS

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

(Filed September 10, 1973)

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION AND SOLGAR CO., INC.,

Plaintiffs,

-v-

CASPER W. WEINBERGER, Secretary of Health, Education and Welfare and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

NOTICE OF MOTION

73 Civ. 3448 (MEF)

S I R S :

PLEASE TAKE NOTICE, that upon the pleadings and a certified copy of the record on file with this Court, and upon all prior proceedings had herein, the defendants will move before the Honorable Marvin E. Frankel of this Court on September 17, 1973 at the United States Courthouse, Foley Square, New York, New York, or as soon thereafter as counsel may be heard, for an order, pursuant to Rule 12(b) of the Federal Rules of Civil Procedure dismissing this action and for such other and further relief as the Court may deem to be just in the circumstances.

Dated: New York, New York
September 6, 1973

Yours, etc.,

PAUL J. CURRAN
United States Attorney for the
Southern District of New York
Attorney for Defendants

By: /s/ [redacted]
[redacted] L. [redacted]
Assistant United States Attorney
Office and Post Office Address:
United States Courthouse
Foley Square
New York, New York 10007
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TO: BASS & ULLMAN
Attorneys for Plaintiffs
342 Madison Avenue
New York, New York 10017

REPLY AFFIDAVIT OF JOSEPH JOHN VITALE
UNITED STATES DISTRICT COURT (Filed September 12, 1973) 92a
SOUTHERN DISTRICT OF NEW YORK

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,

Plaintiffs,

-against-

CASPER W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

Index No. 73 Civ. 3448

REPLY AFFIDAVIT

STATE OF NEW YORK)
) SS.:
COUNTY OF NEW YORK)

JOSEPH JOHN VITALE, being duly sworn, deposes and says:

I am Professor of Community Medicine and Professor of Pathology at the Boston University School of Medicine; Director, Nutrition Programs, Boston University Schools of Medicine; and Senior Research Pathologist at the Mallory Institute of Pathology in Boston; and Professor of Medicine and Nutrition, Facultad de Medicina, Universidad de Antioquia, Medellin, Colombia. Previously I held the position of Professor of Nutrition at Tufts University School of Medicine. In addition, I was an Associate in Nutrition and then an Assistant Professor of Nutrition at the Harvard School of Public Health. I have also been Professor of Nutrition in the School of Medicine and in the College of Agriculture of the University of Wisconsin. Also, for two years I was a Visiting Professor of Nutrition at the School of Medicine,

Universidad del Valle, Cali, Colombia. During this time I was Scientific Director of a Cooperative Program in Nutrition between the Department of Nutrition at Harvard and the School of Medicine in Colombia.

I have taught courses in nutrition for many years. These included a three-month elective in nutrition research and training at the Universidad de Antioquia. I have also participated in providing lectures in nutritional pathology, within the Department of Pathology, at Tufts and at Harvard Medical School and participate in the nutrition teaching program at the Harvard School of Public Health. Finally, I have taught nutrition and the pathophysiology of malnutrition to the graduate students of the Frances Stern Nutrition Center at the Tufts-New England Medical Center. I have also been affiliated with the Frances Stern Nutrition Center which includes a clinic where outpatients are seen by therapeutic nutritionists as well as physicians, and where the patients' total nutritional needs are met and they are instructed in dietary management. I am also called upon by physicians to consult on nutritional problems.

Annexed hereto is a copy of my curriculum vitae which includes over 50 scientific articles published by me in the areas of public health, clinical and basic nutrition.

I am constantly in touch with the medical and scientific literature in the field of nutrition and keep current in the area by constant reading of articles on the subject in leading medical and scientific journals.

On the basis of my scientific experience, including

research, clinical and teaching experience, and my study of the medical and scientific literature, I am led to the conclusion that the recent regulations published by the Food and Drug Administration requiring a prescription for Vitamins A and D at levels above 10,000 IU and 400 IU respectively have no scientific basis. In matter of fact there is no scientific evidence to even support any possible contention of toxicity at levels at three to five times the Recommended Daily Allowance for said vitamins.

The letters submitted by the Food and Drug Administration do not constitute scientific evidence contrary to the statements I have just made. For example, the letter of January 22, 1973 of Dr. George V. Mann (Exhibit D) contains no supportive references or rationale for his singular conclusion that all vitamins shall be put on a prescription requirement. If we were to adopt the philosophy propounded by Dr. Mann, as I understand it from his letter, it would necessarily follow that almost every over-the-counter product, except perhaps toothpaste or hair tonic, should be put on a prescription basis. It is this philosophy which has greater concern for me as a scientist and as a citizen than the regulations themselves which are presently before this Court. It is my opinion that a great deal of confusion is being created in this proceeding by discussing questions of toxicity and danger when in reality we are being presented with discussions of philosophy.

To the same effect, the other letters submitted by the FDA do not constitute scientific evidence of toxicity or danger

at any levels which are being discussed in the present regulation.

I am firmly in support of proper controls over products distributed to the American public. I also believe that there should be requirements for complete and accurate information about all products, in proper labeling, to both the professions and to the laity. I take exception, however, to the instant proposal for prescription requirements which I do not consider to be based upon scientific fact.

/s/
JOSEPH JOHN VITALE

Sworn to before me this
11th day of September, 1973.

ROBERT ULLMAN
Notary Public, State of New York
No. 30-4051700
Qualified in Nassau County
Commission Expires March 30, 1975

Curriculum Vitae

Name: Joseph John Vitale

Present Position:

a) Professor of ~~Nutrition~~ Pathology, Dept. Path.
Department of Preventive Medicine and Pathology
b) Director, Nutrition Programs
~~Boston~~ Tufts University School of Medicine
c) Senior Research Pathologist
Mallory Institute of Pathology
Boston City Hospital
d) Professor of Medicine and Nutrition
Facultad de Medicina
Universidad de Antioquia
Medellin, Colombia

Professor of Community Medicine
Department of "

Date & Place of Birth: December 14, 1924 - Boston, Massachusetts

Citizenship: U.S.A.

Marital Status: Married

Academic Training

Dates	Institution	Degrees
1947	Northeastern University (Biology)	B.S. (Boston)
1949	New York University (Medical School Physiology)	M.S. (N.Y.)
1951	Harvard School of Public Health (Nutrition)	Sc.D. (Boston)
	Harvard Medical School (Biochemistry)	
1966	Universidad de Antioquia	M.D. (Colombia)

Positions Held

Dates	Position	Institution or Agency
June - Sept. 1949	Toxicologist	Massachusetts Department of Public Safety
1951 - 1960	Research Assistant	Mallory Institute of Pathology
1951 - 1966	Research Associate in Nutrition	Harvard School of Public Health

Positions Held (cont.)

Dates	Position	Institution or Agency
1960 - 1962	Assistant Professor of Nutrition; Visiting Professor of Nutrition, Cali, Colombia	On leave - working on a Cooperative Program in Nutrition between the Department of Nutrition HSPH and the School of Medicine, Universidad del Valle, Cali, Colombia
Feb., 1966 Oct., 1967	Professor of Nutrition Research Associate	College of Agriculture School of Medicine University of Wisconsin
1963 - Present	Co-Director, ~~Tufts~~ B.U. Antioquia Collaborative Nutrition Program	

Member of:

Sigma Xi (1954)
American Institute of Nutrition (1955)
British Nutrition Society (1956)
American Association for the Advancement of Science (1963)
American Society of Clinical Nutrition (1964)
American Public Health Association (1964)
Latin American Society of Nutrition (SLAN)

1959 Special consultant to Interdepartmental Committee on Nutrition for National Defense (ICNND) for Nutrition Survey in South Vietnam (3 months duration).

1959 Visiting lecturer, University of Tokyo Medical School

1959 Claude Bernard Professorship Award for the year 1959 (University of Montreal)

1960 Special consultant to ICNND for Nutrition Survey in Colombia

1960 - 1962 Scientific Director of Cali-Harvard Nutrition Project (Universidad del Valle, Facultad de Medicina, Cali, Colombia)

Invited Chairman, Scientific Session, Sixth International Congress of Nutrition. Edinburg, Scotland, 1963 (August 9 - 15)

Invited Speaker, Seventh International Congress of Tropical Medicine and Malaria. Rio de Janeiro, Brazil, 1963 (September 1-10)

Director of Summer Medical Student Program, 1963. Organized Summer Medical Research Program for seven second-year Harvard medical students in Cali (4) and Medellin (3), Faculties of Medicine, Colombia.

Director of Summer Medical Student Program, 1968. Summer Medical Research Program for three first-year and one fourth-year Tufts University School of Medicine medical students, in Medellin, Colombia, at the Universidad de Antioquia.

Co-Scientific Director, Medellin, Colombia-Harvard Nutrition Cooperative Program (1964-1966). As a result of these co-operative programs between the Department of Nutrition and the Faculties of Medicine; Dr. Vitale makes several trips a year to work in the Department of Medicine.

1966-1967 Co-Principal investigator (U.S.) of Medellin - Wisconsin collaborative Programs (now continuing from Boston).

1967 - Present Co-Director ~~Tufts~~ B.U.-Antioquia Nutrition Program. Dr. Hernan Velez, Co-Director from Antioquia Facultad de Medicina.

Latin American Associations:

The Cali-Harvard Cooperative Nutrition Program began on September 1, 1960. During the year preceding 1960, a number of conferences had been held between Dr. Stare, Chairman of the Department of Nutrition at the Harvard School of Public Health and the Dean of the School of Medicine in Cali, Colombia, to discuss the desirability of appreciably expanding a cooperative program in nutrition in Cali, Colombia. As a result of these conferences, it was decided that it would be mutually advantageous to develop a strong Department of Nutrition in the School of Medicine at Cali. With funds made available by the Rockefeller and Kellogg Foundations and with various personnel from the Department of Nutrition, Harvard University, efforts were directed toward increasing the activities of the new Department of Nutrition, officially organized on October 1, 1960. Dr. Joseph J. Vitale, Assistant Professor of Nutrition at Harvard, took a leave of absence and was in residence in Cali for approximately two years. The progress reports of the Cali-Harvard Nutrition Project are available.

During the Cali-Harvard Program basic clinical research and public health programs, a course in clinical nutrition, a metabolic unit, and pre-kwashiorkor clinics in communities were established. The new Department of Nutrition developed strong ties (collaborative programs) with several other departments including parasitology,

Surgery, Pathology, Pediatrics, Medicine and Preventive Medicine. Out of these programs came several publications published in the English medical literature.

Dr. Vitale has visited and given lectures at various institutions in Latin America. He speaks Spanish fluently.

The Cali-Harvard Program terminated in 1963 and Dr. Vitale was asked to develop a similar program at the Universidad de Antioquia, Facultad de Medicina, Medellin, Colombia. Since 1963, Dr. Vitale has been engaged in a cooperative nutritional program in collaboration with various members of the medical faculty in Medellin. Dr. Hernan Velez, Associate Professor of Medicine is the director of the nutrition program in Medellin. Several collaborative programs are now in existence. There is a four bed adult metabolic unit and an eight bed pediatric unit in Medellin at the University Hospital. This unit is for the study of nutritional diseases; e.g., anemias, malabsorption, kwashiorkor and others. In addition, the Nutrition Program maintains a study in a nearby village, Heliconia, where the effects of a food supplementation and a health service program on physical and mental development and on morbidity are being studied. Dr. Vitale spends approximately two months a year in Medellin. The Tufts-Medellin Nutrition Program also provides training in public health nutrition for Tufts and Antioquia medical students.

As in Cali, the Tufts-Antioquia Program has excellent rapport with most of the other medical school departments and enjoys excellent collaborative support from them.

Publications

Thermochemical efficiency of growth. J. Mayer, J. J. Vitale, and T. K. Taira. Nature, 167:532, 1951.

Mechanism of the regulation of food intake. J. Mayer, J. J. Vitale, and M. W. Bates. Nature, 167:562, 1951.

Free selection of nutrients by hereditarily obese mice. J. Mayer, M. M. Dickie, M. W. Bates and J. J. Vitale. Science, 113:745-746, 1951.

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Interrelations between pantothenic acid, protein and calorie intakes with respect to respiration and morphology of duodenal mucosa. J. J. Vitale, D. M. Hegsted, J. Di Giorgia, and N. Zamchek. Metabolism, 2:367, 1953.

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The effect of thyroxine on magnesium requirement. J. J. Vitale, D. M. Hegsted, M. Nakamura and P. Connors, J. Biol. Chem., 226: 597, 1957.

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Studies of interrelationships between dietary magnesium and calcium in atherogenesis and renal lesions. J. J. Vitale, E. E. Hellerstein, D. M. Hegsted, M. Nakamura and A. Farbman. Am. J. Clin. Nutr., 7:13, 1959.

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Dr. Joseph J. Vitale has also presented numerous papers at scientific meetings (Federation Society meetings, A.S.C.N. meetings, etc.) and has had many abstracts published which are not listed.

Joseph J. Vitale and D. Mark Hegsted. Effects of Dietary Methionine and Vitamin B_{12} Deficiency on Folate Metabolism. British Journal of Haematology. 17:467, 1969.

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EXCERPTS FROM RECORD CERTIFIED BY DEFENDANT SCHMIDT IN DISTRICT COURT

HOFFMANN-LA ROCHE INC.

NUTLEY • NEW JERSEY • 07110

February 9, 1973

Hearing Clerk
Department of Health
Education and Welfare
Room 6-88
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Re: Proposed Statement of Policy - Vitamin A and Vitamin D - Federal Register, December 14, 1972

These comments are in connection with the above-referenced Notice of Proposed Rule Making which appeared in the Federal Register for Thursday, December 14, 1972 as corrected in the Federal Register of Thursday, January 4, 1973.

Hoffmann-La Roche Inc., a New Jersey corporation, is an "interested person" within the meaning of the above Notice, since it is a major manufacturer and supplier of bulk vitamins and is also a manufacturer and seller of both ethical and proprietary vitamin products.

1. GENERAL CONSIDERATIONS

In general, the thrust of the subject proposal is that limits should be set on

non-prescription levels of vitamins A and D because of toxicity questions. Our basic contention is that the questions raised by this proposal should be held pending a complete review by the appropriate OTC Drug Review Panel.

Our comments on the actual toxicity question are mainly directed to vitamin A, but it is our impression that vitamin D might be allowed on a non-prescription basis at a higher level than the suggested 400 I.U. without presenting significant toxicity problems.

While there are certain differences between vitamins A and D which give rise to a greater degree of concern with the latter, such as the fact that hypervitaminosis D in general provides symptoms which are more serious than those seen with Vitamin A, and the lower level of reversibility of hypervitaminosis D effects as opposed to those found with vitamin A, most likely comments will be received from other interested persons exploring the question of vitamin D toxicity in greater detail.

We recognize that both vitamin A and vitamin D when taken in excessive doses can cause toxicity problems, but the proposal largely ignores the issue of the actual levels which give rise to toxicity problems. While we share the desire to protect the public with regard to misuse of these vitamins, on the other hand,

any steps taken in this direction should be reasonable and scientifically sound based on the best available medical knowledge.

2. ACTION ON THIS PROPOSAL SHOULD AWAIT THE COMPLETION OF THE OTC DRUG REVIEW

The present proposal specifically states:

> "All vitamins are included among the over-the-counter drugs to be reviewed by an OTC Drug Advisory Review Panel...."

The present proposal is based on questions of toxicity only, and appears to be adopting an interim position until all issues in connection with these vitamins are fully aired by the appropriate OTC Drug Review Panel. We regard it as far more advisable to resolve all questions relating to specific vitamins at one time rather than to pursue them in a piecemeal fashion.

The adoption of the present proposal obviously would require reformulation and relabeling of a great many products. Should the OTC Panel ultimately reach different conclusions from those presented in this proposal, manufacturers would then be presented with these problems a second time. In the absence of some compelling necessity, this double burden should be avoided.

We no way suggest or imply that matters of convenience and expense to industry should predominate over questions of hazard to the public health. In the case of Vitamin A, at least, no such hazard has been shown requiring precipitate action.

Preparations containing Vitamin A at very high dosage levels have been marketed for many years. Now, with the OTC review nearly at hand, it is suddenly determined that a hazard exists requiring that action be taken. Having waited for twenty years or more it is difficult to see why we cannot wait another year or so for the completion of the OTC review. In fact, not only is there no greater hazard today than there was five years ago, ten years ago, fifteen years ago, or twenty years ago, but rather there is less hazard.

Based on a DESI notice published in the FEDERAL REGISTER of August 19, 1971, FDA notified industry by letter of January 12, 1972, that Vitamin A preparations containing 50,000 I.U. of Vitamin A would, among other things, have to be labeled for "prescription use only". Only a little more than a year ago Vitamin A preparations containing 50,000 I.U. or more were freely available to the general public, whereas today such preparations can only be obtained on a physician's prescription. As will be seen from the literature compilation to be discussed later, Vitamin A toxicity symptoms linked to dosages of less than 50,000 I.U. daily have been quite rare.

In view of the FDA action noted above, it is difficult to understand the statement in the preamble to the present proposal that: "At present vitamin A is available over the counter in dosage levels as high as 50,000 I.U. per dosage unit." If such products are being shipped in violation of the "prescription only" requirement, it would appear that FDA has ample authority to act without having to adopt the proposed policy statement.

It should be noted that, at least to the best of our knowledge, industry did not oppose FDA's action in limiting Vitamin A preparations containing 50,000 I.U. or more per dosage unit to prescription status only. We believe that this lack of opposition can be attributed to a recognition by industry that it was a reasonable limitation in the interest of the public health.

In summary, we contend that both the consumer and industry will be better served by delaying action on the present proposal and leaving the matter to a complete review by the OTC Drug Review Panel.

3. THE MEDICAL LITERATURE ON HYPERVITAMINOSIS A IN MAN DOES NOT SUPPORT THE PRESENT PROPOSAL

The Food Nutrition Board, National Research Council, National Academy of Sciences has concluded: "If large doses of vitamin A (20 to 30 times RDA) or of

carotene are ingested for long periods of time, manifestations of toxicity develop." Recommended Dietary Allowances (7th Ed. 1968), p. 23. It would appear that the conclusion of the Food Nutrition Board is generally supported in the literature with some exceptions.

In connection with this proposal, we have made a thorough review of the medical literature relating to hypervitaminosis A in man. The information from these articles has been summarized and compiled in tabular form. Attached hereto as Table 1 is a compilation of 72 articles on this subject. Also attached is a Table 1 Supplement which includes a compilation of 12 additional articles. All 44 articles included on the FDA bibliography referred to in the proposal are included in these compilations and are indicated by asterisks in column 1 of the tables.

We have analyzed the data in the articles included in Table 1 as to various factors involved in hypervitaminosis A. The articles in the Table 1 Supplement were not included in the analysis because the latter articles were not readily available and they were compiled at a later point. However, the additional articles cited in the Table 1 Supplement do not result in any significant alterations in the results of the analysis of the first 72 articles. It should be added that these articles rely almost entirely on subjective evaluation of data

obtained through patient histories. There is reason to believe, especially in cases of parental overdosing, that the actual daily dosage levels of vitamin A were underestimated.

a. Body Weight

With hypervitaminosis A the relationship between body weight and the number of units ingested daily appears to have some significance. Unfortunately it is rather difficult to make a completely accurate evaluation of this factor based on the references in the literature because in many cases the weight of the patient was not indicated. In order to get some feeling for this, however, we did look at those cases where weights were supplied and in cases where the weight was not given reference was made to a table of weights appearing in Textbook of Physiology and Biochemistry, Bell, Davidson, Scarborough (6th Ed.) pp. 1096-97.

The most significant finding in looking at the data in this way was that there were only a few cases where the daily dosage of vitamin A throughout the period of ingestion was less than 2,000 I.U. per kilogram of body weight. (Table 1, Nos. 15,23,24,30,31,38,40,52, and 53) Even here one of the cases (Table 1, No. 23) involved administration of vitamin A by I.M. injection. In another case, (Table 1, No.30) the history of the intake was in doubt and in two other cases (Table 1, Nos. 31 and 52) the amounts taken were not judged

to be toxic. It should be added that in most cases the amounts taken ranged up to levels far in excess of 2,000 I.U. per kilogram of body weight.

b. Age

A review of the literature compiled in Table 1 on the basis of age would tend to reinforce the hypothesis that body weight is a more important factor than age. Hypervitaminosis A symptoms have been noted in very young infants as well as in an individual over 65 years of age. A compilation of 110 cases in the medical literature relating hypervitaminosis A to age results in the following data:

HYPERVITAMINOSIS A BY AGE

No. Cases		Age of Subject
6		3 months or less
12		3 months - 1 year
16	57%	1 - 2 years
16		2 - 4 years
13		4 - 12 years
18		12 - 18 years
13		18 - 30 years
9	43%	30 - 50 years
7		over 50 years
110		

As can be seen there is a fairly even distribution among the various age groups noted, but there seems to be at least a preponderance of cases in children below 12 years of age.

c. Duration of Intake

Another important factor to be considered is the duration of the intake of excesses of vitamin A. Again it is difficult to establish clearly the total relationship among factors such as body weight, level of dosage and duration of intake, however, it should be noted that based on a study of 107 cases from the articles compiled in Table 1, 70% involved intake duration in excess of four months. Following is a summary of these 107 cases in terms of duration of the vitamin A intake:

HYPERVITAMINOSIS A - DURATION OF INTAKE

No. Cases		Duration of Intake
7		1 week or less
4	30%	1 week to 4 weeks
12		1 month to 4 months
10		4 months to 6 months
23		6 months to 1 year
26	70%	1 to 2 years
17		2 to 5 years
7		5 to 10 years
1		over 10 years

Based on the above data the general observation may be made when hypervitaminosis A has been encountered it has usually been associated with long-term ingestion.

d. Levels of Daily Ingestion

An analysis of 107 cases from the articles included in Table 1 reveals the following in terms of the daily intake involved.

HYPERVITAMINOSIS A - LEVEL OF DAILY INTAKE

No. Cases		Estimated Daily Intake, Orally
7		600,000 IU A or more
5		500,000 - 599,000 IU A
11	(78%)	400,000 - 499,000 IU A
12		300,000 - 399,000 IU A
24		200,000 - 299,000 IU A
24		100,000 - 199,000 IU A
16	(15%)	50,000 - 99,000 IU A
8	(7%)	Under 50,000 IU A
107		

As can readily be seen 78% of the cases involve estimated daily intakes of 100,000 IU or more. Only eight cases or 7% involve estimated daily intakes of less than 50,000 IU of vitamin A. Of the latter eight cases seven were infants and only one was an adult. A closer look at these cases is warranted.

Taking the cases of children first, a 29 month old child was given an estimated dosage of 37,500 IU of vitamin A for 510 days. The indication was that the vitamin A was administered in the form of a natural fish oil concentrate, probably oleum percomorph, which not only contained 60,000 IU of Vitamin A

per gram, but 8,500 IU of vitamin D per gram as well (Table 1, No. 3). A 12 month old child was given at least 25,000 I.U. of vitamin A daily for a period of 273 days (Table 1, No. 58). An infant weighing only 2.1 kg was given 12,000 IU of vitamin A daily in the form of multi-vitamin drops for a 7 day period (Table 1, No. 59). Four of these cases were treated together in the literature (Table 1, No. 68). They involved a 2 1/2 month old infant, a 3 1/2 month old infant and a 5 1/2 month old infant all of whom were given an estimated 22,500 IU daily for 60, 25 and 74 days respectively and a 4 month old infant who was given an estimated 17,500 IU of vitamin A for 98 days. In each of these cases it appears that liquid preparations were involved and that such preparations contained fairly substantial amounts of vitamin D as well as vitamin A.

The one case (Table 1, No. 30) involving hypervitaminosis A in an adult at an estimated dosage intake of less than 50,000 IU per day was that of a 62 year old woman. As stated by the author, because of the woman's neurotic state the patient history was in doubt and it is possible that the actual amount of vitamin A she was ingesting daily was underestimated. In this case it was indicated that the woman was taking high doses of vitamin A for a period of approximately eight years.

There are two cases reported in the literature involving adults who were ingesting an estimated 50,000 IU of vitamin A daily. The first of these (Table 1, No. 31)

involved a 79 year old man who had been taking vitamin A at a level of 50,000 IU daily for 17 years. While his liver did have a high vitamin A content there were no obvious signs or symptoms of vitamin A toxicity. The second case (Table 1, No. 53) involved a 54 year old man who had been ingesting 50,000 IU of vitamin A daily for approximately 3 years. This man was a house painter and it is not entirely clear that his symptoms were all related to vitamin A, since, because of his occupation, there was exposure to fumes from paint and solvents.

e. Types of Preparations and Reasons for Excessive Ingestion

Looking at the literature compiled in Table 1 as it relates to children, there are 60 cases. It is interesting to note that of these cases 17 involved overdoses with oleum percomorph a fish oil preparation which contained 60,000 IU of vitamin A and 8,500 IU of vitamin D per gram. Seven other cases involved oleum percomorph together with other products. Most of the cases reported on children involved liquid preparations and in many of them vitamin D was involved as well. Thirty-eight of the sixty cases were caused by parental over-dosing, six were caused by physicians prescriptions followed by parental over-dosing, and the remaining 16 cases were caused by physicians recommendations and/or treatment procedures.

There were 47 cases reported in the literature tabulated in Table 1 on adults. In 27 of those cases the preparation used was not reported, in 16 cases the product involved was a 50,000 IU preparation, in two cases emulsions were involved, in one case 25,000 IU tablets were taken, and in one case vitamin A was given by injection.

An analysis of these cases indicates that in 20 of them there was an initial prescription by a physician followed by self-medication, in 14 cases prescription or treatment by a physician was involved, and only 13 of the cases were entirely based on self-medication.

f. Miscellaneous Observations

There are two further points to be noted. The literature review fails to reveal any instances of mortality resulting from excessive consumption of commercial vitamin A preparations. Secondly, the reports in the medical literature do not support a finding that there has been a significant increase in the number of medical reports on hypervitaminosis A in man in recent years.

HYPERVITAMINOSIS A MEDICAL REPORTS BY YEAR *

1939 - 1	1955 - 3	1965 - 6
1944 - 1	1956 - 3	1966 - 3
1947 - 1	1958 - 2	1967 - 2
1948 - 2	1960 - 2	1968 - 3
1950 - 6	1961 - 4	1969 - 2
1951 - 7	1962 - 1	1970 - 6
1952 - 7	1963 - 2	1971 - 4
1953 - 4	1964 - 3	1972 - 6
1954 - 3		

* 84 medical literature references from Table 1 and Table 1 Supplement, including some general review articles which do not report new cases.

g. Conclusion

The present FDA proposal starts with the premise:

> "Large doses of vitamin A ... ingested over long periods of time can cause adverse effects, some of which are serious."

There is general agreement as to the truth of that statement and the data from the medical literature would confirm this. Other than the arbitrary selection of 10,000 IU of vitamin A, as the limit for non-prescription status, however, the proposal nowhere attempts to answer the question of the level of vitamin A which can actually cause problems. An analysis of the data would tend to support the action already taken by FDA in placing vitamin A dosage forms containing 50,000 IU or more per dosage unit on prescription only. There is certainly nothing in the literature which would support a limit of 10,000 IU of vitamin A per dosage unit in adults. While the data tend to support a lower limit in children's preparations than with adult preparations, with children it is liquid preparations which are generally implicated and this proposal offers little if anything, which would curtail misuse of such preparations.

4. THE ARTICLES IN THE FDA BIBLIOGRAPHY RELATING TO VITAMIN A STUDIES IN ANIMALS DO NOT SUPPORT THE PRESENT ACTION

A review of a number of the articles included on the FDA's list of articles pertinent to vitamin A toxicity studies in animals reveals little, if any, support for the

position taken in this proposal. Attempts at extrapolation of data from studies in rats and other animals to humans is tenuous at best and is not warranted in connection with this proposal.

Many of the articles refer to problems caused by vitamin A deficiencies rather than simply those caused by excesses of vitamin A. See "Fetal Death and Maldevelopment Resulting From Maternal Vitamin A Deficiency in the Rat," Proc. Soc. Exp. Biol. & Med. 72: 687 (Dec. 1949); "Excessive Vitamin A and Congenital Abnormalities," J.A.M.A. 153: 1176 (Nov. 28, 1953); "Disturbance of Embryonic Development by Maternal Vitamin Deficiencies," J. Cell. Comp. Physiol. 43: 208 (May 1954); "Vitamins and Hormones," 18: 552-554 (1960); "Effect of Vitamin A Deficiency or Excess on the Oxidative Phosphorylation by Rat Liver Mitochondria," J. Biol. Chem. 241(5): 1229-1232 (Mar. 10, 1966); and Giroud, A., Fed. Proc. 27(1): 172-3 (Jan, Feb, 1968).

Other articles dealing with excessive vitamin A as the cause of congenital abnormalities involve administration of very large amounts of vitamin A. For example, 35,000 I.U. daily administered via stomach tube to rats, "Excessive Intake of Vitamin A as a Cause of Congenital Anomalies in the Rat," Science 117: 535-536 (May 15, 1953); 75,000 to 150,000 I.U. on the ninth, tenth or eleventh

day of pregnancy in rats, "Congenital Hypervitaminosis A," Nutrition Reviews 17(9): 276-277 (Sept. 1959); 15,000 I.U. by intraperitoneal injection in mice, "Malformations of the Mouse Fetus Caused by Hypervitaminosis A...," Arch. Env. H. 10: 732-41 (May 1965); 50,000 to 125,000 I.U./kg. of body weight in beagles, "Teratogenicity of Vitamin A in the Canine," Fed. Proc. 26: 486 (Mar-Apr 1967); 120,000 I.U. or 600,000 I.U. of vitamin A before malformed rat fetuses occurred, "Problem of Embryotoxicity of Vitamin A," Dtsch. Tierarztl. Wschr. 78: 294-6 (May 15, 1971) (Ger.).

These are representative examples from the FDA's list of articles on vitamin A studies in animals. The animal data in these articles is not in accordance with human experience. To duplicate in humans the doses given to animals in these studies on a kilogram of body weight basis, would require truly massive doses many times in excess of the 10,000 I.U. limitation in the present proposal. In addition, such factors as differences in metabolism and gestation periods cannot be ignored. While these articles may be interesting scientifically, they do not appear to have any bearing on the present issues, especially since there are a number of articles previously discussed relating to vitamin A experience in humans.

5. IF ACTION ON THE PROPOSAL IS NOT DELAYED PENDING THE OTC DRUG REVIEW THE VITAMIN A LIMIT FOR ADULTS SHOULD BE RAISED TO 25,000 I.U.

While the best course would be to delay action on the present proposal until a complete review is made by the appropriate OTC Drug Panel, if the decision is

to act sooner, the proposed 10,000 I.U. limit on vitamin A is too low for adults. As shown in our review of the literature, symptoms of vitamin A toxicity have rarely been implicated in cases where persons were ingesting less than 50,000 I.U. per day and in most cases the levels have been substantially higher.

It is recognized that children are affected at lower dosage levels than adults, probably because of lower body weight. Accordingly, if action is to be taken on the present proposal, we suggest that the 10,000 I.U. limitation be retained in preparations designed for young children, but contend that the limit for adult preparations should be raised to 25,000 I.U.

In both cases, these levels would not only be safe in themselves for the subject groups, but also would provide a wide margin of safety. We would consider these suggested limits to be realistic based on the substantial body of medical knowledge reported in the literature in connection with vitamin A toxicity. These levels would also maintain in each group upper level limits of approximately the same ratio in terms of multiples of the RDAs. If necessary, adult preparations containing more than 10,000 I.U. up to and including 25,000 I.U. of vitamin A could be appropriately labeled to indicate that their use is restricted to "Adults only" and other appropriate precautions could also be included.

We must continue to recognize the inherent right of the American people to self-medicate where this can be done safely. The approach suggested above

would accomplish this by providing safe dosage levels to persons who desire to take higher levels of vitamin A without forcing them either to take multiple doses of lower dosage forms or having to visit physicians in order to obtain prescriptions. If further safeguards are considered necessary to protect against accidental ingestion by children, the possibility of using safety closures could be considered.

6. THE PROPOSAL COULD HAVE A NEGATIVE NUTRITIONAL EFFECT

The ten-state nutrition survey conducted during the 1968-1970 period by the Department of Health, Education, and Welfare revealed a high incidence of low vitamin A values among important segments of the United States population. See for example "Highlights from the Ten-State Nutrition Survey," Nutrition Today, July/August 1972. In most cases the nutritional needs of the subject groups would be met by ingestion of RDA levels of vitamin A and we do not suggest that most individuals would need daily levels of vitamin A in excess of RDA's in order to meet their nutritional requirements.

We do suggest that a great many people are uneasy in matters of health, especially where quesitons of toxicity are raised. In view of the prestige of the FDA among consumers, wide-spread publicity to the effect that FDA considers relatively low levels of vitamin A toxic, creates the possibility that at least some consumers

would overreact to such announcements and deliberately avoid ingesting any vitamin A. Even such a widely-used food as margarine is specifically labeled to contain 15,000 I.U. of vitamin A per pound. Thus, problems of vitamin A deficiency in the population could become more prevalent.

To avoid creating misinterpretation and undue apprehension in connection with vitamin A, any limitations imposed because of questions of toxicity should not be set at unreasonably low levels. Any limitations must be realistic in light of actual levels which do cause toxicity problems, while maintaining a reasonable margin of safety.

7. PROMOTION OF HIGH LEVELS OF VITAMINS A AND D

Part of the rationale for the proposed Statement of Policy as expressed in the subject notice is "that there is widespread promotion to the laity of excessive quantities of these vitamins for prophylaxis and treatment of a variety of diseases and disorders." We submit that to the extent distributors of vitamins engage in improper promotional activities there is adequate statutory and regulatory authority in the federal agencies having jurisdiciton to curtail such activities. Also mentioned is the fact that high doses of vitamin A have been recommended "in the lay press, on radio, and on television." To the extent that recommendations are made by those claiming expertise in nutrition who are not directly engaged

in the distribution of vitamins, such recommendations, where improper, should be countered by expanded efforts on the part of FDA to educate the consumer. Reputable manufacturers and distributors of vitamin products should not be held accountable for statements of others over whom they have no control and such situations should not serve as a rationale for new regulations. Such a regulatory philosophy would place reputable manufacturers in all fields at the mercy of commentators recommending misuse of their products.

The proposed policy statement would do little to eliminate such problems as may exist, since it will not eliminate unfounded nutritional recommendations "in the lay press, on the radio, and on television". Those who wish to accept such advice will simply take multiple doses of lower dosage forms or will seek prescriptions from physicians.

8. IF THE PROPOSED ACTION IS NOT DELAYED PENDING THE OTC DRUG REVIEW THE TIME ALLOWED FOR COMPLIANCE IS INADEQUATE

Under the present proposal only sixty (60) days are allowed after final promulgation, beyond which time noncomplying products could not be labeled or dispensed without being subject to regulatory proceedings. If action on this proposal is not delayed to allow a complete OTC Drug Panel Review, this time

period is far too short. It would not only result in severe economic loss to those having substantial inventories of vitamin A products in amounts greater than 10,000 I.U., but would also be difficult to meet in terms of reformulation and relabeling.

No time period would be too short if there were a genuine hazard to the public health, but, as pointed out elsewhere in these comments, no such hazard presently exists, especially in view of action already taken by FDA limiting dosage forms of vitamin A to "prescription only" status at the 50,000 I.U. level.

CONCLUSION

The present proposal should be held or withdrawn pending the outcome of the OTC review. The medical literature on vitamin A does not support a finding of hazard to the public health requiring action at this time, especially in view of the fact that products containing 50,000 I.U. or more have already been limited to prescription status.

If action is not stayed until the completion of the OTC review, the proposed non-prescription limit of 10,000 I.U. of vitamin A per dosage unit should

be retained only for preparations intended for children and for adult preparations the non-prescription limit should be 25,000 I.U. of vitamin A per dosage unit. Such limits would not only provide dosage forms which are safe in themselves for the indicated age categories, but would, in each case, also provide a wide margin of safety. In any event, a longer period of time should be allowed to effect any changes imposed.

Respectfully submitted,

HOFFMANN-LA ROCHE INC.

By E. B. Anderson
Vice President

Submitted in Quintuplicate
Certified Mail, R.R.R.

Table I

HYPERVITAMINOSIS A in MAN

Author(s) and Reference	Form of Product	Mode of Administration	Estimated Dosage	Duration	Toxicity (salient symptoms)	Cause, Origin or Reason for Toxicity	No. of Pts.	Age	Sex
1. H.W. Josephs, ★ Amer. J. Dis. Child. 67:33-43, 1944	natural vitamin A halibut liver oil	orally	@ 240,000 U.S.P. units daily on occasion drank oil from bottle in undetermined amounts mother's statement	@ 2 yrs, 9 mos	hepatomegaly, splenomegaly, hypoplastic anemia, leukopenia, increased serum vitamin A, increased serum lipids, advanced skeletal development, clubbing of fingers, sparse, coarse hair, abnormal appetite for halibut liver oil	parental overdosing and accidental consumption, probably also received vitamin D from oil	1	3 yrs	M
2. J.A. Toomey & ★ R.A. Morissette, Amer. J. Dis. Child. 73:473-480, April, 1947	natural vitamin A oleum percomorph	orally	@ 250,000 U.S.P. units daily — 500,000 U.S.P. units daily one or two teaspoons full daily mother's statement	@ 20 mos on lower dose and @ 3 mos on higher dose	hepatomegaly, increased serum vitamin A, increased serum lipids, bone abnormalities, increased serum phosphatase, low serum proteins, sparse, coarse hair, avid appetite for butter, pain and localized periosteal swellings	parental overdosing and accidental consumption, child was also given vitamin D (35,000-70,000 units) daily. Abnormally fond of butter	1	23 mos	M
3. B.H. Berrey, Pediatrics 6: 78-85, 1950	natural vitamin A probably oleum percomorph	orally	@ 37,500 I.U. daily 30 drops of natural fish oil concentrate daily mother's statement	@ 1 yr, 5 mos	postinfantile hyperostosis with subdural hematoma, hyperirritability, photophobia, fatigue, fever, anemia with leukocytosis, external thickenings of the corticallis of the bones	incorrect dose was given, child also received vitamin D (5,355 I.U. daily)	1	29 mos	F

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4. J. Caffey, ★ Pediatrics 5:672-688, 1950	natural vitamin A oleum percomorph or Drisdol + A or Navitol	orally	@ 100,000 - 600,000 I.U. daily mother's or father's statements	@ 6 mos - 17 mos	infantile cortical hyperostosis, increased serum vitamin A	parental overdosing, gave oleum percomorph instead of cod liver oil. Three children also received vitamin D (20,000-40,000 units daily)	7	12-37 mos	5 M, 2 F
5. C.T. Fried & M.J.H. Grand, ★ Amer. J. Dis. Child. 79:475-486, March, 1950	natural vitamin A oleum percomorph	orally	@ 400,000 - 500,000 I.U. daily mother's statement	@ many months-over 1 yr	infantile cortical hyperostosis, greatly increased serum vitamin A also received vitamin D from oil	parental overdosing and accidental consumption, gave oleum percomorph instead of cod liver oil. One child ate excessive amounts of butter	2	16 mos 2 yrs	M
6. T.C. Wyatt, C.A. Carabello & ★ M.E. Fletcher, JAMA 144:304-305, Sept. 23, 1950	natural vitamin A oleum percomorph	orally	@ 400,000 - 500,000 I.U. daily mother's statement	@ 2 yrs	anorexia, tenderness of extremities, low grade fever, generalized pruritus, weakness, pronounced irritability, pale skin, unsteady gait, x-ray changes of long bones, high serum vitamin A, upper respiratory infection	parental overdosing in the form of oleum percomorph, child was also given vitamin D (60,000 - 70,000 units daily)	1	3 yrs	F
7. J.M. Arena, ★ P. Sarazen, Jr., & C.J. Baylin, Pediatrics 8:788-794, 1951	vitamin A oleum percomorph + ABDEC drops	orally	@ 80,000 - 82,500 U.S.P. units daily mother's statement	@ 2-1/2 mos	anorexia, hyperirritability, craniotabes, high serum vitamin A	physician's prescription, child was also given vitamin D (11,000-11,500 U.S.P. units daily)	1	6-1/2 mos	F

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8. C. Bair, JAMA 146:1573-1574, 1951 *	vitamin A oleum percomorph	orally	@ 240,000 units grandmother's statement	@ 3 mos	pruritus, irritability, pain, swelling of bones, high serum vitamin A, cranial hyperostosis	grandmother overdosed child. The child also showed an avid appetite for dairy products (butter, milk, cheese), also ate tomatoes and sweet potatoes	1	28 mos	M
9. D. Gribetz, S.H. Silverman & A.E. Sobel, Pediatrics 7: 372-385, 1951	vitamin A oleum percomorph or Infadol	orally	@ 100,000 + U.S.P. units daily 240,000 units daily history by parents	@ 1-1/2 yr @ 7 mos	irritability, lip fissures, sparse, coarse hair, pain in extremities, high serum vitamin A, thickening of bones (cortical hyperostosis), elevated serum alkaline phosphatase	incorrect doses, were given. One child was also given vitamin D (20,000 U.S.P. units daily)	2	17 mos 2-1/2 yrs	1F 1M
10. I.E. Rineberg & B.T. Gross, JAMA 145:1222-1225, July 28, 1951	vitamin A Navitol	orally	@ 185,000 units daily mother's statement	@ 9 mos	infantile cortical hyperostosis, pain in limbs, frequent nose bleeds, upper respiratory infection	parental overdosing. The child also was given vitamin D (37,500 units daily)	1	33 mos	F
11. M.B. Sulzberger & M.P. Lazar, JAMA 146:788-793, June 30, 1951 *	vitamin A capsules of 50,000 IU	orally	@ 600,000 units daily and 1,000,000 - 2,000,000 on special occasions patient's statement-advised by radio nutrition commentator"	@ 18 mos	tenderness of various bones, slight bilateral exophthalmos, warm and dry skin, sparse, coarse hair, chloasma or Riehl's melanosis-like pigmentation, menstrual changes, pruritus, slight fissuring of nasal apertures and corners of mouth, acneform lesions on face, nails were soft and brittle, onychorrhexis, absence of radiologic changes of the bones	self medication	1	44 yrs	F

Table I

12. S.E. Goldzier, II, J.C. Pisacano & A.M. Wald, J. Pediat. 41: 198-201, 1952 *	natural vitamin A oleum percomorph	orally	@ 150,000 units daily for 4 mos and 300,000 units daily for 2 months mother's statement	@ 6 mos	hyperirritability, dry, coarse skin, thickening of extremities, hepatonegaly, high serum vitamin A, cortical hyperostosis, tenderness of bones	parental overdosing. Child was also given vitamin D (21,600-43,200 units daily)	1	24 mos	F
13. J.F. Naz & W.M. Edwards, New Engl. J. Med. 246:87-89, 1952	vitamin A oleum percomorph	orally	@ 220,000 units daily mother's statement	@ 8-1/2 mos	hyperirritability, anorexia, constipation, pruritus, sparse hair, palpable indurated swelling of head, lips dry and cracked, tenderness and brawny thickening of forearms, liver 2-1/2 finger breadths below right costal margin	parental overdosing. Child was also given vitamin D (31,680 units daily)	1	9 mos	F
14. G.C. Reyersbach, J. Hanelin & R.J. Joplin, New Engl. J. Med. 246:978-980, 1952	vitamin A oleum percomorph	orally	@ 240,000 units daily physician's recommendation	@ 1 yr	anorexia, irritability, pruritic skin rash, subcutaneous tender swelling, pain of the extremities, cracked dry lips, sparse, coarse hair, cortical hyperostoses, and a high vitamin A serum level	physician's prescription. Child also had an avid craving for butter	1	3 yrs	F
15. E. Bifulco, New Engl. J. Med. 248:690-692, 1953 *	vitamin A unreported source	orally	@ 100,000 I.U. daily as revealed by patient's history	@ 4 yrs	insomnia, coarse hair, loss of hair, pain in joints, exophthalmos, weakness, loss of weight, anorexia, pigmentation of forehead, bleeding from mucous membranes	physician's prescription	1	52 yrs	F
16. A.G. Knudson, Jr., & P.E. Rotheman, Amer. J. Dis. Child. 85:316-334, 1953 (cite a case of Dr. Mary Malloy)	natural vitamin A oleum percomorph	orally	@ 62,500 units daily mother's statement	@ 3 wks	tremors in extremities, bulging fontanelle, liver edge could be felt 3 cm below costal margin, high serum vitamin A	parental overdosing. Child was also given vitamin D (25,500 units daily)	1	7 wks	F

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17. E.W. Shaw & J.Z. Niccoli, Ann. Internal. Med. 39:131-134, 1953 ★	vitamin A capsules of 50,000 or 25,000 IU	orally	@ 200,000 - 275,000 I.U. daily patient's comment - "took capsules in lieu of a meal"	@ 2 mos	marked asthenia, 10 lb. weight loss, anorexia, polydipsia, polyuria, a skin rash, excessive hair loss over entire body, soreness and fissuring of lips, pain in shoulder joints, ribs, tibia and ankles, high serum vitamin A	self medication	1	25 yrs	M
18. A. Gerber, A.P. Raab & A.E. Sobel, Amer. J. Med. 16: 739-745, 1954 ★	vitamin A vitamin A only, preparation unreported	orally	@ over 500,000 units daily taken with hospital staff knowledge for a skin condition	over 8 yrs	severe headaches, visual disturbances, bone pains, pruritus, fissuring and soreness of mouth, alopecia, pigmentation of skin	self medication blood level 2000 mcg/100 ml highest ever recorded	1	28 yrs	F
19. R.A. Elliott, Jr. & R.L. Dryer, JAMA 161:1157-1159, 1956 ★	vitamin A capsules of 10,000 and 50,000 IU	orally	@ 160,000 - 180,000 units daily patient's comment with improvement she increased dosage	@ 7 mos	bone and joint pain, fatigue, insomnia, swelling of ankles, ecchymosis, soreness of the mouth with blisters on the tongue, frequency of urination, hepatomegaly, tibial tenderness, high serum vitamin A	self medication but previously initiated by a dermatologist's prescription for acne	1	21 yrs	F
20. R.W. Hillman, Amer. J. Clin. Nutr. 4:603-608, 1956	vitamin A aqueous emulsion-Aquasol A	orally and I.V.	@ 1,000,000 units daily and 2,000,000 units daily @ 1,000,000 units daily	@ 13 days and 1 day 25 days	clinical picture resembled that of accidental vitamin A poisoning	experimentally induced	1	40 yrs	M
21. D.W. Creek, K.J. McNiece & L.M. Nelson, Amer. J. Gastroenterol 29:169-172, 1958	vitamin A Aquasol A in 2 cases-unknown in 3rd	orally	1 pt took 150,000 units daily 2 pts took 200,000 units daily patient extended medical recommendation	over 2 yrs 1 pt over 2 yrs 1 pt over 5 yrs	alopecia, anorexia, malaise, petechial and ecchymotic hemorrhages into the skin and mucous membranes	initially prescribed by dermatologist, physician or ophthalmologist & treatment extended or dosage increased by patient	3	16 yrs 17 yrs 17 yrs	1 F 1 M 1 M

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22. T.K. Oliver, Jr. & W.H. Havener, ★ Arch.Ophthalmol. 60:19-22, 1958 and ★ T.K. Oliver, Jr. in J. Dis. Child 95:57-68, 1958	vitamin A unreported source	orally	@ 200,000 units daily superficial non-pitting acne not improved significantly by vitamin A treatment	@ 10 mos	leg pain, scanty menses, scaling and cracking of lips, fissuring of corners of mouth, limp, dry hair, maculopapular eruption on trunk and desquamation of palms and soles, hyperirritability, moderate alopecia, early papilledema in both eyes, tenderness in extremities, high serum vitamin A	physician's prescription and self medication, denying advice of subsequent physician	1	14 yrs	F
23. G. Morrice, Jr., ★ W.H. Havener & F. Kapetansky JAMA 173:1802-1805, 1960	vitamin A unreported source	orally and I.M.	@ 90,000 units daily - 200,000 units daily patients received vitamin A as an acne treatment	@ 10 mos to 4 yrs	double vision, scaling lesions on hands and legs, fissures at corners of mouth, scaling of lips, alopecia, hyperirritability, 14 lb. weight loss, irregular menses, headache, nausea, anorexia, bilateral papilledema, somnolence, splenomegaly	physician's prescription and druggist's recommendation	3 (1 prev. reported by Oliver)	14-16 yrs	F
24. W.W. Stimson, ★ New Engl. J. Med. 265:369-373, 1961	vitamin A unreported source	orally	@ 100,000 units daily originally as an acne treatment	@ 5 yrs	abdominal pain, anorexia, nausea, fatigue, hip and tibial pain, hepatosplenomegaly, dry lips, leukopenia, sparse hair, high serum vitamin A	physician's prescription and self medication	1	32 yrs	F
25. W.K. Woodard, ★ L.J. Miller & O. Legrant, J. Pediat. 59: 260-264, 1961	vitamin A Trivisol	orally	@ 71,500 units daily misinterpretation of pediatrician's instructions	@ 4 mos	increased intracranial pressure, bulging fontanelle, vomiting, irritability, drowsiness, hyperostosis of clavicles, tender subcutaneous swellings, spotty alopecia	parental overdosing	1	4 mos	M

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6. C.W. Pease, JAMA 182:980-985, 1962	vitamin A Navitol or oleum percomorph	orally	excessive dose of A + D concentrate (teaspoon range est. 50,000-500,000 units daily)	@ 6-14 mos	retardation of growth and early closure of epiphyses in addition to the acute symptoms of toxicity; growth of legs seriously impaired	parental overdosing teaspoonfuls misinterpreted in place of drops	7	13 mos 7 yrs	6 F, 1 M
7. C.F. Burgoon, Jr., J.H. Graham, F. Urbach & R. Musgnug Arch. Dermatol. 87:63-80, 1963	vitamin A Aquasol A	orally	@ 300,000 U.S.P. units daily-600,000 U.S.P. units daily	@ 5-7 mos	insomnia, anorexia, headache, pruritus, dry skin, scaling lips, elevated serum vitamin A	physician's prescription	3	16-46 yrs	2 M, 1 F
8. J. Soler-Bechara & J.L. Soscia, Arch. Internal. Med. 112:462-466, 1963	vitamin A tablets of 25,000 IU	orally	@ 75,000 - 150,000 units daily - 375,000 units daily	@ 8 yrs	fatigue, weight loss, bone and joint pains, bone tenderness, loss of body hair, pruritus, dry skin, hepatosplenomegaly, anemia, headache, and skin rashes	self medication to improve vision and for tiredness	1	39 yrs	F
9. J.M. Smith, Oral Surg., Oral Med., Oral Pathol. 17:305-307, 1964	vitamin A unreported source	orally	@ 300,000 units daily	@ over 6 mos	swollen, bleeding, and tender gingivae, dry, scaly lips, itching, painful shins, anorexia	self medication increasing prescription of physician by 6 times original potency	1	14 yrs	M
10. S.S. Bergen, Jr., & P.A. Roels, Amer. J. Clin. Nutr. 16:265-269, 1965	vitamin A numerous preparations	orally	@ 33,333 I.U. daily + 8,714 I.U. from food daily vague history by patient - patient's neurotic state judged to interfere with her ability to relate	@ 8 yrs	sparse, coarse hair, pale, dry, scaly skin, edema in lower leg, erythema and hemorrhages in leg, fissuring of shank of leg, tenderness of joints, pain in bones, high serum vitamin A	self medication a food faddist	1	62 yrs	F

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31. R.F. Krause, Amer. J. Clin. Nutr. 16:455-457, 1965 *	vitamin A unreported source	orally	@ 50,000 I.U. daily as supplement	@ 17 yrs	no obvious signs and symptoms of vitamin A toxicity; high vitamin A content in liver	self medication because it was "good for him"	1	79 yrs	M
32. H.I. Lecks & D. Baker, Clin. Pediat. 4: 32-37, 1965	vitamin A unreported source	orally	@ 100,000 units daily - 400,000 units daily	@ 14 mos	possible pseudotumor cerebri vitamin A intoxication symptoms	incorrect dose was given reason not clear	2	4-1/2 yrs 9-1/2 yrs	1 F, 1 M
33. H. Shatin, Arch. Dermatol. 92:331, 1965	vitamin A unreported source	orally	@ 400,000 units daily	@ 6 mos	papilledema in the left eye	physician's prescription for keratosis follicularis	1	42 yrs	M
34. R.J. Di Benedetto, JAMA 201:700-702, 1967 *	vitamin A unreported source	orally	@ 600,000 units daily	@ 3 yrs	fatigue, pain in joints and legs, pruritic, dry, scaly eruption of skin, marked edema, sparse, coarse hair, alopecia, yellowish skin, palpable liver, high serum vitamin A	self medication for maxillary sinusitis	1	51 yrs	F
35. W.B. Shelley & D.M. Carter, Arch. Dermatol. 95: 652-653, 1967	vitamin A unreported source	orally	@ 250,000 units daily	@ 4-1/2 mos	high serum vitamin A, pain in bones, headache, nervousness, persistent diarrhea	physician's prescription for Darier's disease	1	16 yrs	M
36. J. Jowsey & B.L. Riggs, J. Clin. Endocrinol. 28:1833-1835, 1968	vitamin A unreported source	orally	@ 200,000 units daily	@ 1 yr, 6 mos	headache, subacute papilledema, fatigue, dry, scaling skin, cracked lips, muscle stiffness, generalized pruritic rash, chronic paronychia about the toenails, high serum vitamin A, increased alkaline phosphatase activity, bone changes	self medication following physician's prescription, 300,000 I.U. for 1 month	1	18 yrs	F
37. B.P. Lane, Amer. J. Pathol. 53:591-598, 1968	vitamin A unreported source	orally	@ 50,000 units daily- 5,000,000 units daily	@ 5 yrs	moderate prolongation of prothrombin time and increase in serum alkaline phosphatase activity	self medication a food faddist	1	24 yrs	M

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38. J.A. Madsen & A. Linker, J. Pediat. 75: 843-852, 1969	vitamin A Aquasol A liquid or capsule	orally	@ 50,000 units daily - 65,000 units daily - 100,000 units daily	@ 4 mos - 14 mos	fatigue, irritability, hepatosplenomegaly, abdominal distension with massive ascites, high serum vitamin A, fall in serum albumin, increased seizures	physician's treatment for 4 different syndromes	5	3-1/2-18 yrs	1 F, 4 M
39. M.S. Fedotin, ★ JAMA 212:628, 1970	vitamin A tablets 50,000 I.U.	orally	@ 150,000 units daily	@ 4 yrs	pseudotumor cerebri, pappilledema and diplopia, high serum vitamin A	physician's prescription for acne 4 years previously	1	18 yrs	F
40. M.H. Feldman & ★ M.S. Schlezinger, Arch. Neurol. 22: 1-7, 1970	vitamin A unreported source	orally	@ 100,000 units daily - 500,000 units daily	@ 3-1/2 - 4 yrs	headaches, cracking lips, facial eruption, palpable liver, papilledema, benign intracranial hypertension, diplopia, high serum vitamin A	incorrect dose given and self medication for skin condition	2	20 yrs	1 M, 1 F
41. A.D. Lascari & W.E. Bell, Clin. Pediat. 9: 627-628, 1970	vitamin A unreported source	orally	@ 200,000 units daily - 300,000 units daily	@ 1 yr	pseudotumor cerebri, papilledema, headaches, double vision	self medication as therapy for facial acne	1	15 yrs	F
42. L. Rubin, ★ A.L. Florman, T. Degnan & J. Diaz, Amer. J. Dis. Child. 119:132-138, 1970	vitamin A cod liver oil + multivitamin drops	orally	@ 400,000 units-625,000 units weekly	@ 4-1/2 yrs	hepatosplenomegaly, hepatic disfunction, hypersplenism	parental overdosing, one pint of cod liver oil and 1-1/2 bottles of multivitamin drops weekly	1	6 yrs	F
43. M.D. Muenter, W.O. Perry & ★ J. Ludwig, Amer. J. Med. 50: 129-136, 1971	vitamin A Aquasol A and unreported sources	orally	@ 100,000 I.U.-200,000 I.U. daily 400,000 I.U. daily, then 200,000 I.U.-300,000 I.U. daily	@ 1-1/2 yrs @ 1 yr @ 8 yrs	fatigue, dry, cracking skin, pain in bones, anorexia, pruritus, headache, high serum vitamin A, palpable liver, sparse hair	self medication following original prescription of 300,000 I.U. for one month or 100,000 I.U. for 3 months	1 1	18 yrs (previously reported by Jowsey) 52 yrs	F F

Table I

44. R.C. Wieland, F.H. Hendricks, F. Amat Y Leon, L. Gutierrez & J.C. Jones Lancet 1:698, 1971	vitamin A unreported source plus multivitamin preparation	orally	@ 105,000 units daily and 300,000 units every 4th or 5th day + A&D ointment	@ 6 mos	lethary, swollen tender cervical lymph nodes, polydipsia, polyuria, hypercalcemia	self medication for acne pt. also took vitamin D (400 U. daily)	1	16 yrs	M

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45. L.B. Dickey & E.J. Bradley, Stanford Med. Bull. 6:345-348, 1948	vitamin A Mavitol cod liver oil Vi-penta Squibb's vitamin A	orally	@ 400,000 U.S.P. units daily + butter and other food rich in vitamin A	@ 18 mos	pruritus, pain in upper extremities, swelling on scalp, restlessness, thin, coarse hair, hepatomegaly, tenderness of bones, high serum vitamin A, high alkaline phosphatase activity	parental overdosing. Child was also given vitamin D (14,000 + U.S.P. units daily)	1	36 mos	F
46. P.E. Rothman & E.E. Leon, Radiology 51:368-374, 1948	vitamin A oleum percomorph Vi-penta	orally	@ 125,000 units daily 75,000 units plus daily	@ 13 mos @ 6 mos	pruritus, irritability, anorexia, wrist pain, alopecia, fissuring of lips, yellowish skin, painful extremities, difficulty in walking, rash, hepatomegaly, tenderness in limbs, high serum vitamin A	parental overdosing, vitamin D was also given (18,410 units daily)	2	14 mos 22 mos	1 M, 1 F
47. Case No. 623, In Case Reports of Children's Memorial Hospital, Chicago 9:1831-1833, 1951	vitamin A oleum percomorph ABDEC drops	orally	@ 100,000 units daily - 115,000 units daily	@ 9 mos @ 6 mos	irritability, refusal to walk, erythematous, scaly rash on extremities and buttocks, high serum vitamin A, lymphadenopathy, cortical hyperostoses, poor appetite, listless, pruritus fever	parental overdosing. Child was also given vitamin D (14,400 + units daily)	1	15 mos	F
48. J. Caffey, Amer. J. Roentgenology 65:12-26, 1951 (cases were previously reported by J. Caffey in Pediatrics 5: 672-688, 1950.)	natural vitamin A oleum percomorph Drisdol + A	orally	@ 100,000 - 600,00 I.U. daily	@ 6 mos - 17 mos	infantile cortical hyperostosis, increased serum vitamin A	parental overdosing, gave oleum percomorph instead of cod liver oil. Three children also received vitamin D (20,000-40,000 units daily)	7	12 - 37 mos	5 M, 2 F

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49. A.L. Kane, Arizona Med. 9: 29-31, 1952	vitamin A Theragran capsules 25,000 IU	orally	@ 50,000 - 100,000 units daily + milk, butter, green or yellow vegetables	@ 1 yr oleum percomorph Homicebrin + Vigraine capsules prior to 1 year	hepatomegaly, discrete excoriated macular skin rash, high serum vitamin A	parental overdosing mother a registered nurse	1	8 yrs	M
50. _____, Penn. Med. J. 55: 933-934, 1952 (cites case of G.C. Reyersbach, et al; New Engl. J. Med. 246:978-980, 1952)	vitamin A oleum percomorph	orally	@ 240,000 units daily	@ 1 yr	anorexia, irritability, pruritic skin rash, subcutaneous tender swelling, pain of extremities, cracked dry lips, sparse, coarse hair, cortical hyperostosis, and a high serum vitamin A	doctor's prescription for rickets. Child also had an avid craving for butter	1	3 yrs	F
51. M.T. Harrison & R.D. Mercer, Cleveland Clin. Quart. 20:424-429, 1953	natural vitamin A oleum percomorph	orally	@ 200,000 - 400,000 units daily	@ 27 mos	hyperirritability, cheilosis, pruritus, swelling along ulnas and fifth metatarsals, high serum vitamin A	parental overdosing	1	28 mos	M
52. J.D. Gorman, JAMA 155:947, 1954	vitamin A unreported source	orally	@ 50,000 - 100,000 units daily	@ 8 mos	astereognosis and onycholysis not judged to be due to vitamin A toxicity	incorrect dose was given no reason given for dosage	1	50 yrs	F
53. H.S. Bloch, Minnesota Med. 38: 627-632, 1955	vitamin A unreported source	orally	@ 50,000 units daily suspected solvent vapors, patient's report - a house painter	@ 3 yrs	weakness, headache, anorexia, fever, hepatomegaly, absent patellar reflex on the left and atrophy of the quadriceps muscle, neurtic pain in left hip and thigh, intestinal bleeding	physician's prescription and continued self medication for eczema	1	54 yrs	M
54. E.B. Tudor, Journal Lancet 75: * 372-373, 1955	vitamin A Navitol with viosterol	orally	@ 200,000 units daily	@ 8 mos	craniotabes; irritability, sparse hair, high serum vitamin A	parental overdosing	1	20 mos	M

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55. C.A. Turtz & A.I. Turtz, * Amer. J. Ophthalmol. 50:165-166, 1960	vitamin A unreported source	orally	@ 200,000 units daily	@ 18 mos	headaches, blurred vision, occasional attacks of diplopia, malaise, pain in joints, superficial hemorrhages throughout the retinae of both eyes, early edema of left disc	incorrect dose given self medication for acne	1	17 yrs	M

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56. W.T. McLean, Jr., Clin. Res. 20(1): 113, Jan., 1972	vitamin A unreported source	orally	@ 150,000 - 200,000 I.U. daily	@15 mos - 26 mos	papilledema, headache, vomiting, high serum vitamin A levels	incorrect dose taken reason not clear	2	adolescents	F
57. R.M. Restak, J. Nerv. Ment. Dis. 155(1):72-75, 1972	vitamin A Hal-Sal	orally	@ 100,000 - 150,000 units daily	@ 6 mos +	depression, insomnia, anorexia, weight loss of 17 lbs., blurred vision, hyperacusis, ataxia, daytime lethargy, toxic psychosis, frontal headaches, amenorrhea, papilledema, high serum vitamin A levels, pseudo-tumor cerebri	incorrect dose taken self-medication for acne	1	18 yrs	F
58. N.J. Siegel & T.J. Spackman, Clin. Pediat. 11(10):580-584, 1972	vitamin A unreported source	orally	@ 25,000 - 57,000 I.U. daily Mother of one a health faddist	@ 9 mos - 1 yr	anorexia, irritability, lethargy, vomiting, stiff neck, inability to walk, increased head size, patchy alopecia, exfoliative pruritic rash, pain in shins, slightly enlarged liver and spleen, elevated transaminase level, elevated serum Ca, markedly elevated serum vitamin A, low protein conc. in CSF, bulging anterior fontanel, increased intracranial hypertension	parental overdosing. One child also received daily 1,000 I.U. of vitamin D, 200 I.U. of vitamin E, 480 mg of vitamin C, 1,600 mg of Ca and 750 mg of PO_4	2	1 yr - 2-1/2 yrs	1 M, 1 F
59. E.L. Greene, Drug Intelligence and Clin. Pharm. 6: 355-360, Oct., 1972	vitamin A multi-vitamin drops	orally	@ 12,000 I.U./day for 7 days an infant of 2100 grams	@ 7 days	increased liver size to 4 centimeters below costal margin, bulging fontanelle, several episodes of projectile vomiting over 8 days, white count was 3,000/cu ml. with 30% neutrophils, hemoglobin was 8.4gm/100ml	incorrect oral dose given inadvertently	1	infant	F

Table I

60. P.M. Gelpke, Can. Med. Assn. J. 104:533, Mar. 30, 1971 *	vitamin A tablet 50,000 I.U.	orally	@ 200,000 units daily taken for acne	@ 2 yrs	headaches, vomiting, diplopia, strabismus, papilledema, CSF pressure grossly elevated	incorrect dose given by pharmacist without time limit	1	15 yrs	F
61. J. Marie & C. See, Amer. J. Dis. Child 87:731-736, 1954 *	vitamin A Vitadone Forte nose drops 50,000 IU/g	orally and nasally (nosedrops)	@ 300,000 - 350,000 units daily	@ 1 - 6 days	vomiting, paleness, lethargic, bulging fontanel, crying, diarrhea, edema	parental overdosing. Four of the patients also received 300,000 units of vitamin D	5	2-7-1/2 mos	1 F, 4 M
62. G. Frontali, Schweiz. Med. Wochenschr. 82(15): 430-433, Apr. 12, 1952 *	vitamin A Asteril	orally	@ 60,000 units daily - 75,000 units daily	@ 214 days @ 100 days	intracranial pressure, projection of the forehead, periosteal thickening of the skull-cap and long bones (cortical hyperostoses) hemorrhagias, anemia, hypoproteinemia, Takata-positive	incorrect dose given. Patient also received 40,000 I.U. of vitamin D daily	1	4 yrs	F
63. J.D. Pickup, Arch. Dis. Child. 31(157):229-232, June, 1956 *	vitamin A avoleum	orally	@ 463,040 units daily - @ 347,280 units daily	@ 42 days @ 730 days	vomiting, anorexia, pain in arms, legs, and forehead, insomnia, weight loss, scaling of skin, cracking of lips, bleeding of lips, enlarged liver and spleen, conjunctivitis, edema of face, alkaline phosphatase elevated, high serum vitamin A levels, shedding of hair, skin rash, elevated plasma Ca and P	incorrect dose given, originally prescribed by a dermatologist and expanded by the Mother	2	4-6 yrs	1 M, 1 F

Table I

64. J. Lyon & J.W. Paulley, Brit. J. Dermatol. 76(2):92-93, 1964	vitamin A unreported source	orally	@ 600,000 units daily lower quantities taken earlier in life	@ 365 days+	headache, tinnitus, vomiting, unsteady gait, papilledema associated with hydrocephalus, lethargic, aching in legs, blurred discs, wasting and weakness of lower limbs, dizzy, some wasting of interossei muscles of the hand	incorrect dose taken for skin condition origin of use and history not clear	1	12 yrs	M
65. W. Raaschou-Nielsen, Dermatologica 123:293-300, 1961	vitamin A palmitate Arovit	orally	@ 300,000 I.U. daily	@ 365 + days	anorexia, weight loss, falling hair from scalp, dry brittle hair, eyebrows and pubic hair thinned, skin felt dry and itchy, fissures of mouth and nostrils, alkaline phosphatase elevated, high serum vitamin A	physician's prescription for skin condition	1	18 yrs	F
66. G. Goeckenjan, et al, Deut. Med. Wochenschr 97: 1424-1429, 1972	vitamin A Mulsin Hochkonzentrat	orally	@ 4,000,000 I.U.	@ 22 days	headaches, dizzy, visual disturbances, vomiting, body weakness, itchy skin, lip and gum changes, scaling of skin, clouding of consciousness for 4 weeks, acute renal failure, hyperglycemia, aplastic anemia, severe infectious complications, high serum vitamin A, hepatomegaly, hypoprothrombinemia, hypercalcemia, hyperlipidemia	physician's prescription for psoriasis	1	30 yrs	M
67. O.F. Jillson, Arch. Dermatol. 93:484-486, April, 1966	vitamin A unreported source	orally	@ 500,000 units daily	@ 60 days	headache	physician's prescription for Darier's disease	1	39 yrs	F

Table I

68.	B. Persson, R. Tunelland K. Ekengren, Acta Paediat. Scand. 54:49-60, Jan. 1965	vitamin A AD-vimin, Astra A-D-ol aquosum	orally	@ 17,500 - 60,000 I. U. daily	@25 - 98 days	anorexia, hyperirritability, edema in head, bulging fontanels, "Sun set" gaze, alkaline phosphatase elevated, high serum vitamin A, exophthalmus, craniotabes, widening of metaphyseal ends, apathy	physician's prescription and parental overdosing, patients also received 3,600-9,000 units daily of vitamin D	5	2-1/2 mos - 5-1/2 mos	2 F, 3 M
69.	P. Ammann, K. Herwig & Th. Baumann, Helv. Paediat. Acta 23(2):137-146, 1968	vitamin A palmitate Arovit	orally	@ 150,000 I.U. daily	@ 730 days	lethargic, anorexia, headaches, vomiting, slight fever, nose bleeds, dry, fissured lips, pain in arms and legs, dry, scaling skin, coarse hair, immobility, elevated alkaline phosphatase, slight hypercalcemia, high serum vitamin A, bone changes, hepatomegaly, hypoprothrombinemia	incorrect dose was given parental overdosing	1	7 yrs 2 mos	M
70.	W. Ehrengut, Z. Kinderheilk. 77(4):468-482, 1955	vitamin A palmitate Arovit	I.M. and orally	@ 187,000 I.U.	@ 2 days	opisthotonus, bulging fontanel, somnolence, moderate edema, petechiae in the face, purulent rhinitis, keratomalacia, hepatosplenomegaly, severe redness of tongue and throat, weight loss, CSF pressure greatly elevated	incorrect dose given. Patient also received 200,000 I.U. of vitamin D	1	4-1/2 mos	M

Table I

71. J.W. Smit & D.P. Hafstede, Ned. T. Geneesk 110:10-11, 1966	vitamin A unreported source	orally	@ 150,000 - @ 300,000 Units daily	@ 18 mos @ 4 yrs	psychic changes, menstrual disturbances, insomnia, thirst, pruritis ani, dryness of skin and mucous membranes, fissuring of lips, falling hair, epistaxis, slight abduction paresis, increased CSF pressure, anemia, leucocytosis, elevated serum phosphatase, feeling of pressure in ears, diffuse pigmentation in the face with hyperkeratosis	self-medication	2	20 - 24 yrs	2 F
72. F.G.I. Jennekens & C.W.M. Van Veelen, Presse Med 74: 2925-2928, 1966 *	vitamin A unreported source	orally	@ 200,000 - 300,000 Units daily	@ 56-913 days	headache, insomnia, hyperirritability, menstrual irregularities, pruritus, urinary incontinence, epistaxis, back joint and extremity pain, diplopia, papilledema, desquamation of the skin, fissuring at corners of mouth, erythema, weight loss, anorexia, EEG - anomalies, hepatomegaly, elevated serum alkaline phosphatase, hemorrhage of fundus, moderate elevation of CSF, slight acceleration in the sedimentation rate, vomiting and nausea	physician's prescription	2	19 - 21 yrs	2 F

Table I Supplement

HYPERVITAMINOSIS A in MAN

	Author(s) and Reference	Form of Product	Mode of Administration	Estimated Dosage	Duration	Toxicity (salient symptoms)	Cause, Origin or Reason for Toxicity	No. of Pts.	Age	Sex
73.	H. Pinkus & R. Hunter, J. Invest. Dermatol. 42:131-136, 1964	vitamin A Vi-Dome-A oral tabs	orally	@150,000 units daily	@ 30 days	retardation of maturation of human keratinocytes	experimentally induced	10	25-40 yrs	7 M, 3 F
74. ★	J.P. Nater & H.M.G. Doeglas, Acta Dermatovener. 50:109-113, 1970	halibut liver (not oil)	orally	@ 2-30,000,000 units daily	@ 1 day	headache, nausea, vomiting, desquamation of face, trunk, hands and feet, immobility, high serum vitamin A levels, elevated lipoid and cholesterol levels, slight increase in LDH	ate too much halibut liver	11	23-61 yrs	11 M
75. ★	S. Silverman, Jr., et al, J. Oral Ther. Pharmacol. 2(1):9-23, July, 1965	vitamin A Vi-Dom-A tablets for oral leukoplakia	orally	@ 600,000 units daily	@ 35 days	dry, itchy, scaly skin, skin rash, photosensitivity, urinary retention, high serum vitamin A levels, altered liver function (elevated BSP & SGOT)	physician's prescription for oral leukoplakia	6	33-83 yrs	2 M, 4 F
76. ★	J. Caffey, Amer. J. Dis. Child. 79:404-405, 1950	percomorph liver oil	orally	large amounts			infantile cortical hyperostosis	4	infants	
	(Dr. H.W. Josephs mentioned)	- has examined 4 more cases since his first report, (Amer. J. Dis. Child. 67:33-43, Jan., 1944)								

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Table I (Supp.)

77. ★	J.M. Cluet-Garcia, Acta Ped. Espan. 9:1448, Dec., 1951		orally	massive doses of vitamins A and D		benign hydrocephalus		1	infant	
78. ★	S.J. Yaffe, et al, Pediat. 48: 655-656, Oct., 1971	general paper; high potency vitamin A preparations can cause serious side effects if taken in excess								
79.	H.R. Getz, et al, JAMA 112(14): 1308-1311, April 8, 1939	vitamin A halibut liver oil for TB	orally	@ 2,000,000 units daily	@ 1 day	dull headache	physician's prescription	4		145a
		vitamin A as carotene	orally	@ 2,000,000 units daily	@ 1 day	dull headache	physician's prescription	1		
80.	T. Dull, et al, J. Clin. Investig. 40:1035, 1961	vitamin A unreported source	orally	@ 200,000 units daily	@ 3 - 4 wks	high serum vitamin A, depressed serum and urinary citrate, decreased serum and urinary calcium, decreased urinary phosphorus	experimentally induced	6 subjects		
81.	J. Cleland & R.V. Southcott, Med. J. Aust. 1(26):1337-1342, 1969	vitamin A husky (dog) liver	orally	large amounts	@ 3 wks	severe skin desquamation, fits, gastrointestinal pain, dysentery, hair loss, anorexia, vomiting, delirium	ate large amounts of husky liver	2 subjects		2 M
82. ★	C. Morrice, JAMA 213: 1344, Aug. 14, 1970	Review paper; refers to papers by Fedotin, Oliver and Havener and Morrice, et al.								

Table I (Suppl)

83. J.R. Frey & M.A. Schoch, Dermatologica 104(2):80-86, 1952	vitamin A acetate Arovit for psoriasis	orally	@ 400,000 - 3,000,000 IU/d	@ 2 days - 6 mos	dryness of the lips, fissuring of the lips, headache, hyperirritability, nausea, scaling of the skin, depapillation and redness on tip of tongue	physician's prescription	9		
84. C.M. Katz & M. Tzagournis, Metabolism 21(12):1171-1176, Dec., 1972	vitamin A for severe acne unreported source	orally	@ 200,000 units daily	@ 2 yrs	anorexia, lethargy, weakness, vomiting, gingival bleeding, 10-lb weight loss, nausea, headaches, stiff shoulders, fasciculation in lower extremities, flaky pruritic rash, epistaxis, loss of some scalp hair, pigmentation of lower abdomen, polyuria, polydipsia, dry, cracked lips, hypercalcemia, tender, palpable liver, EKG showed shortened QT interval and flattened T waves, elevated alkaline phosphatase, high serum vitamin A	self-medication for severe acne	1	18 yrs	M

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March 12, 1973

Miss Beryl McCullar
Hearing Clerk
Food and Drug Administration
Room 6-88
5600 Fishers Lane
Rockville, Maryland 20852

Re: Proposed Statement of Policy
Vitamins A and D, 37 F.R. 26618.

Dear Miss McCullar:

Enclosed are five copies (in four volumes) of comments by Vitaminerals, Inc. on the proposed statement of policy dealing with Vitamins A and D [37 F.R. 26618, December 14, 1972]. Mr. Brandenburg, of the Office of the Associate Commissioner for Compliance, advised the undersigned that these comments could be filed through March 13, 1973.

This submission is divided into four volumes. Volume I contains a summary of Vitaminerals' evaluation of the various articles cited by the Food and Drug Administration, and the additional articles uncovered by Vitaminerals, dealing with the toxicity of Vitamin A. Also included in Volume I are reprints of all the articles collected by Vitaminerals reporting on human toxicity in Vitamin A. Volume II contains reprints of all the FDA authorities, including the FDA animal reports, on Vitamin A. Many of these articles are duplicates of the studies reported by Vitaminerals in Volume I, but are included in the interest of completeness and so that reviewing officials at the FDA can readily cross-reference both volumes in order to confirm the completeness of the work done by Vitaminerals.

Volume III contains Vitaminerals' summary of all the toxicological reports on Vitamin D, as well as the reprints of the articles on Vitamin D as obtained by Vitaminerals.

Volume IV contains reprints of the FDA's articles on Vitamin D, including the animal studies referred to by FDA. Again, Volume IV contains some duplication of the data reported in Volume III, but for the same purpose as before.

Briefly, here is the situation as Vitaminerals sees it. First, with respect to Vitamin A.

VITAMIN A

The preamble to the FDA's proposed statement of policy states that doses of 50,000 I.U. in adults and 20,000 I.U. in infants on a daily basis over long periods are known to produce toxicity. The authorities cited by the FDA and those developed by Vitaminerals support no such allegation. First of all, there are no reported fatalities whatever with Vitamin A at any dosage level. Next, many of the references cited by the FDA are, by their nature, irrelevant to the question of human toxicity. These relate either to experimental studies (incidentally, where no ill effects were shown) or to a bizarre incident where some fishermen ate halibut liver in which the Vitamin A dosage ranged from 2 million to 30 million units in a single dose - hardly a relevant basis for deciding the dietary patterns of the American population.

The remaining studies, involving 64 individuals over a 33-year period, include many cases where the subjects were taking Vitamin A under the prescription of a doctor at very high levels to treat disease conditions. In other words, the doctor was deliberately approaching a very high level of Vitamin A intake in order to achieve a specific result for patients under his care. This would contradict the FDA's argument that the safety of Vitamin A can only be assured by limiting it in high dosages to prescription uses. The side effects cited by FDA in effect were caused by prescription usage and have nothing to do with over-the-counter purchases. Presumably they could occur as well after this regulation as before and the regulation does not purport to reach the problem of using toxic doses in prescription drugs. In any event, the levels ingested were, as the tables in Volume I point out, extremely high, ranging from levels of 100,000 units per day to over a million, and therefore have nothing to do with doses of 50,000 and 20,000 which, FDA says, produce toxic effects.

Moreover, as Vitaminerals points out in Volume I, page 5, many of the toxic reactions were related to peculiar products no longer on the market. One was similar in appearance to cod liver oil and therefore was often mistakenly dispensed, by both physicians and parents, as if it were cod liver oil. Another product was marketed in an ampule which contained 350,000 units, and, because it was in ampule form, appeared to be a single dosage unit, which it was not. Both of these products were reformulated and the problem of potential Vitamin A toxicity disappeared.

Thus, it would appear that the Vitamin A toxicity reports either occurred in prescription usage (where this proposed regulation would offer no protection) or in peculiar product situations no longer in existence, and therefore have no bearing whatsoever on the statement quoted above by the FDA about the level of toxicity of Vitamin A.

One of the studies [H-26, Volume II] deserves special mention. Here the FDA would suggest that the condition of shortening of the leg in infants was caused by dosages of Vitamin A. An examination of the study reveals that it does not support such a conclusion. Seven children are reported on who suffer from this condition. The levels of Vitamin A range from none, in the case of one infant, up to 500,000 units in another. A third infant was receiving the recommended dietary allowances, and the remainder much higher levels, with one unknown. With such a broad range of dosage figures it is obviously scientifically impossible to implicate Vitamin A as the culprit in this situation. Vitamin A is not a constant in these reports.

The FDA also cites a number of animal studies (some of which, mysteriously enough, report on Vitamin A deficiency problems, a subject wholly unrelated to the proposed regulation.) However, animal studies are relevant only if a relationship between the dosage ingested by the animal in a test and a quantitatively anticipated dose in humans can be established. The FDA, in its proposed statement of policy, fails to translate any of the animal data work into human levels. Vitaminerals has, however, done this for each of the studies [Volume I, page 8]. These reveal equivalent dosage levels that are so high as to be meaningless to any human toxicological problem. They range from a low of 4.8 million daily units to a high of 81 million units of Vitamin A.

From all this it can be seen that there is no toxicity data reported by FDA, or discovered by Vitaminerals, which supports any such maximum level as required by the proposed regulation. The incidences of toxicity reported are either irrelevant or at levels tenfold higher than that suggested by FDA to be the case.

VITAMIN D

The Vitamin D data is summarized in Volume III and covers the references cited by the FDA and the additional ones discovered by Vitaminerals. The studies report on 152 subjects over a 32-year period. However, the subjects in study H-1 [Vol. II] must be rejected from evaluation because they were under an experimental efficacy study and, in any event, they suffered no side effects. In another study [D-24, Vol. III], the subjects were not specific and the report does no more than analyze a method for determining a control dose of Vitamin A under prescription for hypocalcemia. The elimination of these two studies leaves 113 subjects for evaluation, and an analysis of those patients appears in Volume III, pages 2 and 3. The great preponderance of these subjects were receiving Vitamin D on prescription, and thus the proposed regulation, limiting OTC usage, would have offered them no protection whatever.

The FDA's suggestion in its preamble that the daily ingestion by infants of dosages between 1,000 and 2,000 I.U.'s has produced hypervitaminosis D is invalid. It is particularly invalid if, as the FDA intimates, a conclusion is drawn that that dosage level is a toxic level. Actually, as the study shows, the reactions cited by FDA occurred in infants who received no Vitamin D [H-3, H-6, D-2, D-26], as well as in infants who were receiving the RDA levels of Vitamin D [H-3].

The agency implies that Vitamin D is a causative factor in infantile hypercalcemia or idiopathic hypercalcemia. (The references cited by the agency are to both). Such an implication is not justified. A thorough and careful analysis of the cited documents reveals that these conditions are

probably genetic in origin and not caused by any specific substance. While it is true that in some of the reports the authors conclude that Vitamin D is associated with these conditions, a careful reading of the actual report reveals a lack of factual support for any such conclusions. The reactions associated with these conditions can occur with no Vitamin D, sub-normal amounts of Vitamin D, RDA levels of Vitamin D, calcium and other substances. Thus, what is implicated here is the presence of Vitamin D in certain unfortunates suffering from this disease condition and the so-called toxic level of Vitamin D has nothing to do with the individual's problem. For these unfortunates the issue is not to avoid a toxic dose of Vitamin D but to avoid it altogether - just as they should avoid calcium (for which FDA sets no maximum limits) and many other substances.

The animal work cited by the FDA is as valueless as the animal work cited for Vitamin A. Translating the figures to anticipated human dosage would develop totals of between two to four million units in one study, and 37.5 million units per day in the other.

Finally, a great many of the articles cited by the FDA are mere reviews of the other articles and, as such, contribute no new specific data. Accordingly, they are not discussed in detail.

In sum, what Vitaminerals has presented is a detailed evaluation, with appropriate charts, of each of the animal and human studies cited by the FDA and those developed by the company. Such an analysis reveals that the levels of ingestion presented by the FDA in the proposed regulation are not toxicologically significant. Since there is no scientific or toxicological basis for the limits imposed by the FDA (the only basis sought here by FDA) we suggest that they are factually unsound and therefore statutorally impermissible.

Very truly yours,

William R. Pendergast

Enclosures
WRP/bmd

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INTRODUCTION

The following comments regarding the proposed statements of policy, Food & Drug Administration, as published in the Federal Register, Volume 137, Number 241, Thursday, December 14, 1972, are herewith filed by Vitaminerals, Incorporated, 1915 Flower Street, Glendale, California 91201.

To facilitate ease of review, we are filing these comments, statements and objections in four separate categories which correspond generally in form to the sequence of statements setforth in the publication in the Federal Register.

I Vitamin A - Human Study

II Vitamin A - Animal Study

III Vitamin D - Human Study

IV Vitamin D - Animal Study

Where references are made to papers, which were not included in the Food & Drug Administration's Bibliography, copies of the complete papers referred to are contained.

As set forth in the Federal Register (Volume 27, Number 241, December 14, 1972) the Food & Drug Administration contends the availability of vitamin A in "high dosage levels without prescription, contributes significantly to their misuse and the occurrence of serious adverse effects". The statement is further made that vitamin A, at levels of 50,000 International Units per dosage unit, is available over-the-counter. Both of these statements are incorrect and not substantiated by the data, either presented in the bibliography or in the Food & Drug Administration's own prior regulation.

The Food & Drug Administration has previously published in the Federal Register, August 19, 1971, new regulations placing 50,000 units vitamin A products on a prescription basis only. These regulations have been in effect since December, 1971. At the present time vitamin A is not available over-the-counter at 50,000 I.U.'s, but contrary to the statement by the Administration, is only available at this level under a prescription legend. The purpose of this limiting regulation, as stated by the Administration when proposed, raised no question of danger to public health, nor serious adverse effects. We respectfully submit, therefore, that the specific statement and the inferences made by the Food & Drug Administration in the proposed regulations of December 14, 1972, are incorrect and are not substantiated by fact.

To support the overall contention of the proposed regulation, the Food & Drug referred to a substantiating bibliography covering the period 1938 to 1971. The following analysis encompasses both this bibliography, supplied by the Food & Drug Administration, and additional references researched by Vitaminerals, Inc. We believe these to be comprehensive and have taken the figures and facts presented by the government and by additional papers to provide the following analysis:

HUMAN STUDIES

One Food & Drug Administration reference was incorrectly identified in the published list (17 - Government Hypervitaminosis A). One paper (9) was unobtainable. Two were (A2 and A27) supplied by Vitaminerals, Inc., and not included on the FDA list.

The references, FDA and Vitaminerals, Inc., covered a 33-year-period - from 1938 to 1971 - and incorporate reports on 145 subjects. This is the bibliography the government contends establishes availability of vitamin A over-the-counter as contributing to adverse effects.

(Note: FDA reference numbers, Hypervitaminosis A are proceeded by "H" to differentiate human studies from animal studies. Vitaminerals' reference numbers are proceeded by "A".

The following had no connection with the Food & Drug's statement, nor this proposed rule making:

11 Fishermen (H39)	These men suffered from adverse effects by ingesting Halibut liver freshly caught aboard their fishing boat.
54 Infants (A26)	These subjects were on an experimental study of vitamin A intake under prescription. There were no ill-effects!
Six Adults (H32)	This was an experimental study on prescription at massive levels which provided some mild effects and is not germane to the question posed.
Ten Adults (A13)	This was an experimental study of vitamin A under prescription showing no ill-effects at high levels.

These three experimental studies and an ingestion of Halibut liver cannot rationally be included in reference to the FDA statments and intent.

The remaining 64 subjects covered in the bibliography fall into five groups:

1) Vitamin A dosage on prescription
2) Vitamin A dosage probably on prescription
3) Vitamin A dosage on prescription with an additional continuing intake or increased level
4) Self prescribed
5) Unknown

1) 16 Subjects: These subjects were taking vitamin A under prescription and while under the supervision of a doctor (References: A2, H7, H10, H13, H18, H21/20/41, H25, H28, H34, A45, H38, H37.

2) 15 Subjects: These subjects were probably taking vitamin A on prescription or direction of their physicians. They were infants and on supplements normally prescribed by pediatricians. Additionally, their intake started at birth when they would be under the care of a pediatrician (Reference: A44).

3) 18 Subjects: These subjects were initially treated with vitamin A under prescription. As noted in the attached summary sheets, they continued use on their own volition; they increased dosage levels of their own volition, they resumed dosage of vitamin A on their own volition, and the dosages was subject to mistake in directions (References: A2, H1, H12, H15, H16, H18, H19, H24, H26, H29, H30, H36).

4) 10 Subjects: These subjects instituted vitamin A therapy of their own vo-

lition, utilizing over-the-counter preparation (References: A1, H14, H22/41, H33, H23, H27, H35, H40, A40, H45).

5) Four Subjects: These four subjects had no known source or specific cause (References: H26, H37).

In review, over a period of 33 years 64 subjects are referred to as being on massive dosage of vitamin A over extensive periods of time. Of these, ten instituted vitamin A dosage of their own volition, four are of unknown origin, 18 continued or modified vitamin A dosage after iniating it under prescription and professional supervision. It would seem the government's contention is difficult to substantiate in light of these factual figures and statements.

DISCUSSION

All the previous referred to subjects were reported on massive vitamin A intake in excess of the unitage levels stated by the Food & Drug Administration. The bibliography does not even support the previous restriction on 50,000 units of vitamin A dosages, even though it was promulgated without reference to potential harm or danger to public health. A comprehensive review of the papers discloses further pertinent facts bearing on this matter.

22 subjects, all of whom received massive dosages of vitamin A under prescription, were utilizing the vitamin product, Oleum Percomorphum, or its equivalent. The majority of the cases established the fact that the similarity of appearance of the product and the package to Cod Liver Oil led to a mistake in directions and the dosage at the "traditional" Cod Liver Oil level, i.e., 1 teaspoonful. At this erroneous dosage and the concentration, A intake was generally between 200,000 to 500,000 I.U.'s, the same pattern of dosage and product follows in the remainder of the papers although not specifically

stated. The error in dosage level was made by mother, druggist, doctors, and in several cases the hospitals. This led to the removal of the product from the market in the early 1950's and its replacement with obvious drop dosage forms to prevent misinterpretation. This cause and the success of removing a packaging and appearance problem can be emphasized by the lack of reported infant cases following that date some 20 years ago (References: A44, A2, H10, H12, H26, A21).

Three infants were reported affected by massive (350,000 I.U.'s) doses of vitamin A prescribed by physicians. The unique packaging, glass ampules, led to overdoses. Because of their appearance the mother considered an ampule as a single dose; since once opened, it was not readily resealable, the entire content was given in single dosages. Two additional infants were purposely given the same dosage, while hospitalized, to duplicate the symptoms. At the suggestion of the pediatrician the product was reformulated to a level of 70,000 units per ampule and "no further problem was encountered" (Reference: H15).

Eight of the subjects took vitamin A over-the-counter at their own volition. The majority of these were dermatological problems, colds, and in two cases one was a food faddist and the other was a psychiatric patient. The most common cause in the remaining subjects was continuation of programs originally prescribed by dermatologists.

In summary, the above and attached analysis of subjects on massive dosages of vitamin A failed to establish the Food & Drug Administration's contention with regard to potential hazards from over-the-counter vitamin A products. An analysis of the papers shows exactly the opposite to be true; that the product, at reasonably high potency levels over-the-counter, provides an exceptional margin of safety. Taken in context with the fact that 2 1/2% of the infants in this country, 2 1/2% of the children in this country, and almost 5% of the adults in this country will suffer mild to severe

reactions from milk, we believe that the safety of reasonably high dosage of vitamin A over-the-counter, has been well established.

PROPOSED POTENCY LEVEL - VITAMIN A

The statement is made by the Food & Drug Administration that doses of 50,000 I.U.'s for adults and 20,000 I.U.'s in infants on a daily basis over long periods of time are known to produce toxicity. The average adverse dose level in the referred papers for infants is 200,000 I.U.'s per day for 8.4 months. The average level for children is 270,000 I.U.'s per day for 26 months. The average level for adults is 293,000 I.U.'s per day for 3.2 years. The minimum in all three categories exceeds the government's figures and in one case (Reference: A32) the 50,000 I.U. level was maintained for 17 years with no untoward effect.

FDA ANIMAL STUDIES

Included in the bibliography under vitamin A Tetrogenicity (referred to as AA reference in summaries attached) were animal studies. With readily available human data on vitamin A levels available, Vitaminerals, Inc., did not pursue papers dealing with animal work. A review of the animal studies is attached. The Food & Drug Administration's bibliography shows six papers not germane to the proposed regulation. Four papers (Reference: AA1, AA3, AA7 and AA16) deal with the effects of vitamin A deficiency on animals. One paper (AA23) cannot be realted to any dosage levels and the final paper (Reference: AA26) discussed vitamin A Acid, not vitamin A.

The animal studies are not meaningful in a direct reference to human effects as admitted in the papers. This also has been the position of the Food & Drug Adminis-

FDA ANIMAL STUDIES

tration with regard to all submitted animal studies. Therefore, little or no actual information can be drawn from them and in light of existing human studies the data presented is of no import. However, one interesting fact should be noted. If the animal level were translated into approximate human levels, based on a 100 lb. female, the following would be the relative vitamin A intake for a human.

FDA REFERENCE

AA2:	81 million units
AA5:	8.5 million units
AA8:	7.2 to 14.4 million units
AA11:	4.8 to 7 million units
AA12:	24 million units
AA14:	9.6 million units
AA15:	23 million units
AA17:	14 million units
AA18:	6 million units
AA21:	4.5 to 18 million units
AA25:	11.5 to 115 million units

A RATIO OF POTENCY THAT COULD NOT EVEN BE DESCRIBED ADEQUATELY AS MASSIVE.

SUMMARY & RECOMMENDATION

The foregoing data demonstrates the lack of potential harm of vitamin A over-the-counter in adult products. At levels of 50,000 International Units per unit dose, now restricted to prescription, this data holds true. It would seem unwarranted and illogical to promulgate further regulations based on unsupported statements. The

highest level of vitamin A generally available over-the-counter since 1971 has been 25,000 units per unit dose, the safety of which has obviously been well established.

It's our contention that the current, normal maximum levels of vitamin A generally available without prescription, i.e., 25,000 units per day, per dosage unit, should be maintained and provide qualified and proven safe levels.

As set forth in the Federal Register (Vol. 27, No. 241, December 14, 1972), the Food & Drug Administration contends that the availability of vitamin D in an excess of 400 International Units per dosage unit, available without prescription, could cause the possibility of severe irreversible adverse effects.

To support this statement, the Food & Drug Administration referred to a substantiating bibliography covering the period 1938 to 1970.

The following analysis covers both this bibliography, supplied by the Food & Drug Administration, and the additional references researched by Vitaminerals, Inc. We believe these to be comprehensive and have taken the figures and facts presented by the government, and by additional papers, to provide the following analysis:

HUMAN STUDIES

The references, FDA and Vitaminerals, Inc., covered a 32-year-period - from 1938 to 1970 - and incorporate reports on 152 subjects. This is the bibliography the government contends establishes availability of vitamin D over-the-counter as contributing to adverse effects.

(Note: FDA reference numbers, Hypervitaminosis D, are preceded by "H" to differentiate human studies from animal studies. Vitaminerals reference numbers are receded by "D").

The following had no connection with the Food & Drug's statement, nor this proposed rule making:

Nine Infants (H1

These subjects were on an experimental efficacy study - under prescription - and had no side effects.

30 Adults (D24)

These subjects were not specific. The reports covers the determination of a controlling dose of vitamin D under prescription for Hypocalcemia.

These two experimental studies cannot be rationally included in the reference to the FDA's statements and intent.

The remaining 113 patients covered in the bibliography fall into four groups:

1) Vitamin D dosage on prescription.
2) Vitamin D dosage on prescription with an additional qualification.
3) Self prescribed.
4) Unknown Origin

89 Subjects:

These subjects, together with the previously mentioned 39, were taking vitamin D under prescription and while under the supervision of a doctor (references: H3, D2, H11, H12, D8, D9, H14, D21, H19, D16, D24, D22, H21, D-17, D-27, D18, D29).

One Subject:

This subject had no history of any vitamin D intake whatsoever, but was given a vitamin D loading test and showed no sensitivity (Reference: H27).

One Subject:

This subject instituted vitamin D therapy on his own volition (Reference: H5).

22 Subjects:

These subjects had no known source or specific cause (Reference: H5, H6, H8, D7, H16, D25).

In review: Over a period of 32-years, 152 patients are referred to as being on dosages of vitamin D, ranging from sub-normal to massive, over extensive periods of time. One of these specifically instituted vitamin D dosage of his own volition; 22 are of unknown origin; 113 are on prescription - one was on prescription for a vitamin D loading test. The additional 39 on prescription, as reported are not germane to the question.

It would seem the government's contention is difficult to substantiate in light of these factual figures and statements.

DISCUSSION

From the above, the reported cases of adverse effects claimed with vitamin D, the great preponderance of the subjects were taking vitamin D on prescription and under the supervision of a physician, not of their own volition utilizing over-the-counter products.

The government's statement that daily ingestion, by infants, of doses between 1,000 and 2,000 International Units has produced Hypervitaminosis D, usually manifested as infantile syndrome and other symptoms, is not valid. The condition has manifested itself when vitamin D intake was as low as 400 units (H3) and 800 units (D17). Additionally, the condition has manifested itself with no vitamin D intake (H3, H6, D2, D26).

In specific research, infants and children with infantile Hypercalcemia showed the same D plasmal levels as healthy, normal controls of the same age (H16).

The conditions and symptoms mentioned by the Food & Drug Administration have no specific or confirmed connection with vitamin D and the condition occurring in its absence (H2). The conditions described by the Food & Drug Administration thus appear with or without vitamin D (H4, H6, D2, H11, D7).

The incidence of infantile Hypercalcemia or Idiopathic Hypercalcemia, as the study of the bibliography shows, is almost non-existent in this country, where the availability of vitamin D - both on the recommendation of a physician and over-the-counter - is widespread.

The government's statement is misleading, since by inference it involved vitamin D as a causative factor when such is not the case; and researchers have stressed the fact that these conditions are probably genetic in origin and not caused by any specific substance. This is attested to by the familial relationship of infantile Hypercalcemia (Reference H14).

The problems encountered in infantile and idiopathic Hypercalcemia are summed up (Reference: H15) by the fact that in infantile or Idiopathic Hypercalcemia, usually no large amounts of vitamin D are administered and a genetic error of calcium or vitamin D metabolism is suspect. This reaction can occur with subnormal amounts of vitamin D, calcium and many other substances. The conditions described by the Food & Drug Administration is a disease entity of extremely rare occurrence which manifests itself with no D intake, suboptimal intake and high vitamin D intake, with high calcium intake and other unknown substances. It is genetic in origin, its prevention is not amenable to any vitamin D dosage control. The inference of the Administration, as set forth in their proposal, is therefore misleading.

The remaining cases listed attached deal with the utilization of vitamin D, normally at massive dosages and under prescription, to combat the hypocalcemic effects of hypoparathyroidism and prevent the serious advent of tetany. Just as with diabetics and insulin, the vitamin D is balanced out normally at enormous doses for therapeutic effect in maintaining normal calcium level. These can vary from time-to-time, producing minor hypercalcemia but the patients are always returned to maintenance dosages, which have no adverse effects.

The other primary reports included cover resistant rickets, where again massive doses of vitamin D are utilized to prevent permanent skeletal deformities, and at given maintenance dosages have no adverse or permanent effects.

The incidence of these conditions, which are reported with vitamin D levels ranging from none to 400,000 units, attest to the safety of present dosage forms of vitamin D.

SUMMARY & RECOMMENDATION

The foregoing data demonstrates the lack of potential harm of vitamin D over-the-counter in adult products. Based on the data submitted and previous levels of actual human toxicity (Reference: D30), 10,000 units of vitamin D per unit for adult dosages, would provide a well established safety margin. 1200 International Units of vitamin D per unit dose for infants would provide an equally safe margin of dosage level.

BEST COPY AVAILABLE

The FDA Vitamin D Bibliography on Teratogenicity listed two animal studies. The remainder, which covered humans, was transferred to the previously discussed human vitamin D.

While, as in the case of vitamin A, animal studies cannot be directly translated into reactions with humans, taking the dosage levels used in the two studies, the proporational level equivalency for a 100 lb. female would be between two-million to four-million units of vitamin D in one study and 37.5-million per day in the other study. Again, a level which couldn't described as massive but more merely approximates the term monsterous.

R. P. Scherer CORPORATION
9425 GRINNELL AVENUE • DETROIT, MICHIGAN 48213 • AREA CODE 313 871-6100

January 29, 1973

TO: Hearing Clerk
Department of Health, Education & Welfare
Room 6-88
5600 Fishers Lane
Rockville, Md. 20852

FROM: Dr. J. P. Stanley

SUBJECT: Vitamin A and Vitamin D Proposed Statement of Policy.
(Fed. Reg. 12-14-72, pp. 26618-26620)
(Correction - Fed. Reg. 1-4-73, p. 799)

Dear Sir:

The R. P. Scherer Corporation, an interested party who will be adversely affected, offers the following comments to the above Proposed Statement of Policy.

The R. P. Scherer Corporation, 9425 Grinnell Avenue, Detroit, Michigan 48213, incorporated under the laws of Delaware, is a major manufacturer of filled soft gelatin capsules which are used primarily as a dosage form for food and drug products. Over fifty percent of such products are vitamin or vitamin-mineral combinations containing the vitamins A and D. These products are manufactured as special or private formulas for many drug companies, both large and small. Besides the private formula type products, the company also manufactures and maintains stock formulas of these products for sale primarily to the smaller houses. All shipments are made in bulk and are properly labeled.

The above Statement of Policy has a direct bearing on approximately 100 products affecting over 300 companies and would adversely affect this company and over 300 customers by requiring the reformulation and/or relabeling of these products. It is the position of the R. P. Scherer Corporation that:

1. The Statement preempts the OTC review of vitamin and mineral products, which panel of experts will be called upon to decide the issue of safety, (as well as efficacy), for products containing higher than dietary supplement vitamin levels. It is probable that additional reformulation and/or labeling will again be required at that time causing a double burden to the industry within a short time period.
2. Neither the Statement nor the bibliography support the need for immediate action based upon the toxicity of these vitamins and current regulations are sufficient to protect the public until the above-mentioned OTC review. See General Comments below.
3. If the Statement is published prior to the OTC review, either as it stands or is changed in accordance with recommendations similar to those of the R. P. Scherer Corporation, appropriate labeling for such products must be supplied by the FDA and sufficient time allowed (greater than the proposed 60 days) for reformulation and/or the relabeling of inventories. See Specific Comments below.

4. Since the Statement concerns itself solely with the issue of toxicity and if the FDA, after reviewing all comments, still feels the need for urgency then a panel of nutritional experts should be called, immediately, to decide this controversial, scientific issue. This approach to the resolution of scientific issues was the recommended procedure proposed by Mr. Peter Hutt in his talk at the FDLI meeting in Washington, D.C., last December.

Further, it is the contention of the R. P. Scherer Corporation:

1. That 25,000 unit (5X RDA) vitamin A products can be supported from a toxicity standpoint and with use of proper labeling can be marketed OTC to adults (i.e., those over 12 years of age).
2. That the same is true for 10,000 unit (ca. 5X RDA) vitamin A products for children 12 years of age and under, including infants.
3. That on the same basis as A, 2,000 unit vitamin D (5X RDA) products can be supported for the OTC adult market.

GENERAL COMMENTS

1. As regards the preamble of the Statement:

   a. Paragraph 1 concerns itself with the OTC availability of vitamin A at 50,000 units (10X RDA) and of vitamin D at 25,000 units (60X RDA). This is essentially correct for vitamin D but currently, all 50,000 unit vitamin A products require the prescription legend per DESI notice 3444, Fed. Reg. 8-19-71. Until this notice, both products were on the market for approximately 20 years labeled as dietary supplements in accordance with the current law and as the result of the Durham-Humphrey amendment.

   b. The next two paragraphs concern themselves with the position of the American Academy of Pediatrics relative to the toxicity of A and D. Actually, the American Academy of Pediatrics presents little or no toxicity data to support their contentions and fears that products containing less than 50,000 units of A or less than 2,000 units of D are actually hazardous to the general health of the public. Nor do they present evidence to support widespread radio, television and lay press advertising which urges the public to take toxic doses of these vitamins. They even state, ".... the incidence of hypervitaminosis A appears to be increasing." Again, no real evidence. Is this a scientific evaluation of the facts and is the FDA forgetting their scientific image in publishing such comments?

c. The bibliography referred to in paragraph 4 does not support the contention of the FDA that products containing between 10,000 and 50,000 units of A and between 400 and 2,000 units of D are sufficiently hazardous to the health of the general public that such products must be on prescription status.

2. As regards the vitamin A position of the Statement:

a. In paragraph 1, it is stated that "doses of 50,000 units in adults and 20,000 units in infants on a daily basis over long periods are known to produce toxicity."

b. If this is true, it is unscientific, as well as illogical, to allow, as in paragraph 4, a 100% safety factor for infants (20,000 I.U. (10X RDA) toxic vs. 10,000 I.U. (ca. 5X RDA) nontoxic) while adults would enjoy a 500% safety factor (50,000 I.U. (10X RDA) toxic vs. 10,000 I.U. (2X RDA) nontoxic). It is agreed that a 100% safety factor is desirable and sufficient to insure consumer safety. Therefore, 25,000 units (5X RDA) for adults would certainly be warranted as a safe OTC product. The FDA bibliography and the literature would support such limits for OTC products.

R.P. Scherer CORPORATION

3. As regards the vitamin D portion of the Statement:

   a. It is noted that no mer ion is made as to the toxic level for adults as was done with vitamin A, so it would appear that overdosing of infants is the main concern of the FDA as regards vitamin D toxicity. The FDA bibliography and other literature references support levels of 1,200 units (3X RDA) of D for children to 12 years of age and 2,000 units (5X RDA) of D for adults as not being hazardous to the health of the general public.

SPECIFIC COMMENTS

1. Safety of A and D:

   a. Testimony of nutritional experts at the vitamin hearings support the contention that the ingestion of 3 to 5 times the RDA of any vitamin, including vitamins A and D, poses no toxicity problem or health hazard for the general public. See Olson WD-49, p.3 and WD-46, p.5; Vitale WD-65, pp.9,10 and P.651; Stare WD-49, p.4; Mayer WD-46, pp.20,21; Er hoff WD-60-85, p.3; Grollman Tr.2360, 2361; Harrison Tr.23,230-23,234; and Herbert Tr.14,571-14,575. Thus, this definitely supports an OTC product containing a maximum of 25,000 units of A and/or 2,000 units of D for adults and 10,000 units of A and/or

1,200 units of D for children.

b. Our review also supports the safety of an OTC product containing a maximum of 25,000 units of A for adults and 10,000 units of A for infants and children. My summary of this data indicates 53 references, covering 81 cases over a period of 27 years (1944 thru 1971). The vast majority of cases involve extremely high doses of vitamin A over long periods of time.

c. According to Braun (Pediat. Clin. N. America 9, 935 (1962) the toxicity of vitamin A is self-limiting and recovery is prompt. Since excess consumption of any substance can cause toxic effects, perhaps vitamin A can be related in this respect to readily available, potentially harmful foods such as sugar and salt. The latter household table items are potentially harmful to at least certain segments of the population, much as D might be for certain unusually sensitive individuals, but they are not considered harmful for the general public.

d. More specifically, as regards vitamin D toxicity information, you are referred to a somewhat similar proposal on vitamin D published in the Fed. Reg. of 8-28-65, pp.11140-11141. This proposal was never implemented. It is our

belief that comments filed relative to vitamin D toxicity as the result of that proposal are still appropriate today since there has been no significant new evidence published that would establish a need for immediate action at this time. See specifically the submission of the Wisconsin Alumni Research Foundation dated Dec. 27, 1965 and its attachment "Vitamin D in Nutrition."

e. As in the case of vitamin A, (c. above P.651), the 1968 edition of "Recommended Dietary Allowances" published by the Food and Nutrition Board of the National Academy of Sciences (Publication #1694) does not support the position of the FDA that doses of vitamin D of 2,000 I.U. per day or less are hazardous to the general public. They merely point out that for <u>dietary supplementation</u> it is best to leave the level at 400 I.U. However, it is obvious from their toxicity discussion that properly labeled OTC drug products containing up to 2,000 I.U. of vitamin D would be safe for use by the general public.

2. Labeling (Fed. Reg. 12-14-72, paragraph 10, pg. 26619):

a. The statement does not refer to the exact labeling of vitamin A and D containing products. With the recent publication of the tentative order on dietary supplement

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labeling, it will be necessary to develop suitable labeling for current products (intended for 4 years of age and over) containing over 5,000 units of A and over 400 units of D since such products will no longer be labeled as dietary supplements.

b. If the statement stands unchanged, then it should include an FDA acceptable prescription label so that future production of existing products that will become prescription can be properly relabeled.

3. Recommended changes in Statement, ¶ 3._____ Vitamin A preparations for oral use as drugs:

a. No change.

b. In view of ..... in excess of 10,000 I.U. per dosage unit, labeled for use by children up to 12 years of age, or in excess of 25,000 I.U. per dosage unit, labeled for use by those over 12 years of age are drugs subject to ..... sale. Such ..... met:

1. No change.

2. No change (but recommended prescription labeling should be set forth).

c. Preparations containing 10,000 I.U. or less of vitamin A per dosage unit, labeled for use by children up to 12 years of age, or 25,000 I.U. or less of vitamin A per dosage unit, labeled for use by those over 12 years of age, will be ..... exceeds 10,000 I.U. or 25,000

d. Preparations containing over 5,000 I.U. (except approved dietary supplements) but not exceeding 25,000 I.U. of vitamin A per dosage unit are to be labeled as OTC drugs pending the results of the Vitamin-Mineral OTC review. Such products will be regarded as misbranded if the following current label modifications are not met:

1. The label of products containing over 10,000 I.U. of vitamin A per dosage unit or the recommended daily dose is over 10,000 I.U. of A per day must bear a statement "For adults and children over 12 years of age."
2. The label of products containing over 10,000 I.U. of A per dosage unit must bear a warning statement regarding vitamin A toxicity using acceptable wording.
3. To facilitate comparison of products and to fully inform customers, the label of these OTC products must list the name and amount of each vitamin and/or mineral contained therein and the % of the established RDA for each vitamin and/or mineral. The RDAs are standard references for the potency of vitamin products.

e. Vitamin A preparations labeled ..... as of 180 days for prescription products, 1 year for OTC products after day ..... Register.

4. Recommended changes in Statement, ℞ 3._____ Vitamin D preparations for oral use as drugs:

a. No change.

b. In view of ..... in excess of 1,200 I.U. per dosage unit, labeled for use by children up to 12 years of age, or in excess of 2,000 I.U. per dosage unit, labeled for use by those over 12 years of age, are drugs ..... sale. Such ..... met:

1. No change.

2. No change (but recommended prescription labeling should be set forth).

c. Preparations containing 1,200 I.U. or less of vitamin D per dosage unit, labeled for use by children up to 12 years of age, or 2,000 I.U. or less of vitamin D per dosage unit, labeled for use by those over 12 years of age, will be ..... exceeds 1,200 I.U. or 2,000 I.U. respectively.

d. Preparations containing over 400 I.U. but not exceeding 2,000 I.U. of vitamin D per dosage unit are to be labeled as OTC drugs pending the results of the Vitamin-Mineral OTC review. Such products will be regarded as misbranded if the following current label

modifications are not met:

1. The label of products containing over 1,200 I.U. of vitamin D per dosage unit or the recommended daily dose is over 1,200 I.U. of D per day must bear the statement, "For adults and children over 12 years of age."
2. The label of products containing over 400 I.U. of vitamin D per dosage unit must bear a warning statement regarding vitamin D toxicity using acceptable wording.
3. To facilitate comparison of products and to fully inform customers, the label of these OTC products must list the name and amount of each vitamin and/or mineral contained therein and the % of the established RDA for each vitamin and/or mineral. The RDAs are standard references for the potency of vitamin products.

e. Vitamin D preparations labeled ..... as of 180 days for prescription products, 1 year for OTC products, after day ..... Register.

The above comments reasonably set forth our position, contentions and recommendations regarding the referenced Statement of Policy. It is requested that the Commissioner give due note and consideration to these comments and defer action on the issue of Vitamin A and Vitamin D toxicity until its proper consideration during the Vitamin and Mineral OTC review. Otherwise, it is requested that the Commissioner revise the Statement of Policy along the lines of the above recommendations.

Respectfully submitted

R. P. SCHERER CORPORATION

J. P. Stanley

J. P. Stanley, Ph.D.
Technical Director

JPS:bk
enc. (References from Vitamin Hearings listed on page 6 of this submission).

LINUS PAULING
PROFESSOR OF CHEMISTRY

Rec'd December 1972

Routing	Action	Info	Coord
GC-1 (Charles Edwards)	✓		
CM-1		✓	
BF-1		✓	

☐ Prepare for Signature of: ☐ Direct Reply

Remarks:
N/C appl. necessary

Dr. Charles C. Edwards
Food and Drug Commissioner
Department of Health, Education and Welfare
Food and Drug Administration
Washington, D. C. 20204

Dear Dr. Edwards:

I have read in the newspapers that the Food and Drug Administration is proposing to limit the sale of tablets and capsules without a prescription to those containing not more than 10,000 IU of vitamin A.

I think that such a regulation would be asinine - not quite as asinine as to make a similar limit of 100 mg for vitamin C, as was proposed by the Food and Drug Administration on 9 December 1966, but almost as asinine.

I enclose a statement by me opposing the proposed limitation on the sale of vitamin A, and ask that this statement be included in the evidence, and that I also be invited by you to present oral arguments.

Sincerely,

Linus Pauling

LP:ky
enclosure

Statement on the Proposed FDA Regulation Limiting the Sale of Vitamin A

by Linus Pauling
Professor of Chemistry in Stanford University

I am Linus Pauling, now Professor of Chemistry in Stanford University. I was for 42 years at the California Institute of Technology (for 22 years Chairman of the Division of Chemistry and Chemical Engineering), and have taught in Cornell University, Oxford University, University of California, and other universities. I was born in Portland, Oregon, on 28 February 1901, and educated in the public schools of Condon and Portland, Oregon, in Oregon Agricultural College (B.S. in chemical engineering, 1922), and in the California Institute of Technology (Ph.D. in chemistry, minors in physics and mathematics, 1925).

I received the Nobel Prize for Chemistry in 1954, and have received many other awards in chemistry. I also received the 1962 Nobel Peace Prize in 1963, and have a number of other awards for work for peace and better international relations. I also received the Presidential Medal for Merit, the Naval Ordnance Development Award, and several other awards from the United States Government. I also received the Phillips Medal of the American Academy of Physicians, the Modern Medicine Award, and several other medical awards. I am an honorary member of the Harvard chapter of the medical honor society Alpha Omega Alpha, a corresponding member of the French Academy of Medicine, an honorary member of the American Association of Clinical Chemists, an honorary member of the American Society for Pharmacology and Experimental Therapeutics, honorary president of the Academy of Orthomolecular Psychiatry, and a member of about fifty other scientific and medical societies. I have written about 500 papers and a dozen books on physics, chemistry, medicine, and world affairs.

For 35 years much of my work has been on chemistry in relation to medicine. During recent years I have been especially interested in the possibility of achieving a significant improvement in the health of the American people through improved nutrition, with special reference to the proper role of the vitamins.

COPY

The Proposed Regulation of the Sale of Vitamin A

I am opposed to the proposed limitation of non-prescription sale of vitamin A to tablets and capsules containing not more than 10,000 IU for the following reasons:

1. The optimum daily intake of vitamin A is, in my opinion, about 25,000 IU for many people. The FDA has no convincing evidence that this opinion is not correct. The FDA should not make a regulation that interferes with the proper nutrition of the American people.

2. If the proposed limitation of the sale of vitamin A were extended to foods, a prescription would be required for a serving of one half of one ounce of broiled lamb liver or two ounces of sweet potatoes. The FDA is either wrong in proposing the limitation of the sale of vitamin A tablets on capsules or remiss in not also proposing the equivalent limitation of the sale of liver, sweet potatoes, and other foods rich in vitamin A.

3. There is very little chance of damage to humans from ingesting too much vitamin A - far less chance than for many drugs that are sold over-the-counter. The argument that the proposed regulation would significantly protect the American people from a serious danger, that of hypervitaminosis A, is invalid.

4. The proposed regulation would be largely ineffective, and would be economically damaging to the public.

5. The proposed action would, without justification, limit the freedom of the people.

The Optimum Intake of Vitamin A

The optimum intake of a vitamin is the intake that leads to the best of health. This optimum intake is probably different for different persons. The average value of the optimum intake of vitamin A for an adult is not known. I estimate it to be about 25,000 IU per day.

Some evidence to support this value is provided by the work of H. C. Sherman and H. Y. Trupp with rats, Proc. Nat. Acad. Sci. USA 35, 90 (1949). Additional evidence is provided by the consideration of the average amount in a day's ration of 110 raw natural plant foods, in the same way as described for vitamin C in my paper Evolution and the Need for Ascorbic Acid, Proc. Nat. Acad. Sci. USA 67, 1643 (1970), and my book Vitamin C and the Common Cold, 1970. This average for vitamin A is 110,000 IU. When the 16 plant foods with the highest values, above 200,000 in a day's ration, are omitted, the average for the other 94 is 29,000 IU. Even with consideration of the contribution of meat to the diet, there is strong indication that primitive man ingested much more than 10,000 IU of vitamin A per day.

Further evidence that the optimum intake of vitamin A is larger than 10,000 IU per day is that the "therapeutic dose" prescribed by many physicians to improve the health of some patients is usually 25,000 or 50,000 IU per day.

That the optimum intake of a vitamin may be considerably greater than the amount needed to prevent overt avitaminosis or the "recommended daily allowance," which is usually two to five times greater, is shown by the effectiveness of ascorbic acid in amounts 20 to 100 times the "recommended daily allowance" in providing protection against the common cold. The older evidence is summarized in my book Vitamin C and the Common Cold. The new evidence reported by Charleston and Clegg, Lancet 1, 1401 (1972), and by Anderson, Reid,

and Beaton, J. Canadian Med. Assn. 107, 503 (1972), leaves little basis for skepticism.

The Food and Drug Administration, in justice to the American people, could ethically restrict the non-prescription sale to tablets or capsules containing no more than 10,000 IU of vitamin A only if the FDA had convincing scientific evidence that the optimum daily intake for most people, leading to the best of health, were less than 10,000 IU. The Administration does not have such evidence. In fact, the existing evidence indicates that the optimum daily intake is greater than 10,000 IU. It would accordingly be wrong for the FDA to limit the sale of vitamin A in this way.

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Why Should the Sale of Tablets be Restricted and Not That of Foods?

It is proposed that the non-prescription sale of tablets or capsules containing more than 10,000 IU of vitamin A be forbidden, but not that of portions of foods containing more than 10,000 IU of vitamin A.

Either the FDA is wrong in forbidding the sale of the tablets, or it is remiss in not forbidding the sale of a portion of certain foods.

Occasionally I eat a serving of one half pound of liver. According to the book Metabolism of the Federation of American Societies for Experimental Biology, a one half pound portion of raw beef liver contains 100,000 IU of vitamin A, of fried beef liver 121,000 IU, of raw lamb liver 115,000 IU, and of broiled lamb liver 169,000 IU. To be consistent, the FDA should propose restricting the sale by butcher shops and restaurants of beef or lamb in portions greater than half of one ounce (for broiled lamb liver) and 0.8 ounce (for raw beef liver), except when prescribed by a physician.

I also occasionally eat a half pound serving of sweet potatoes. According to the book Metabolism, this serving contains between 18,000 and 45,000 IU of vitamin A. To be consistent, the FDA should restrict the non-prescription sale of sweet potatoes to about two ounces per portion.

There is Little Danger of Hypervitaminosis A

A reason given for restricting the sale of vitamin A is that very large amounts are damaging to the health of human beings.

In fact, there is very little danger of damage through hypervitaminosis A, whereas much damage (ulcers, deaths) is done by aspirin and other drugs that are sold over-the-counter.

So far as I am aware, no person has been killed by taking too many tablets or capsules of vitamin A.

An intake by an adult of 200,000 IU of vitamin A over a period of a year or more has caused some cases of hypervitaminosis A. A somewhat smaller intake, down to about 100,000 IU per day, has caused hypervitaminosis A in infants. A single dose of several million IU causes illness. The disease is brought under control in a few days by decreasing the intake of the vitamin.

Many people have ingested 50,000 to 100,000 IU per day (by eating one half to one pound of liver per day, for example) over long periods of time without developing hypervitaminosis A.

The facts show that the danger of hypervitaminosis A is not great enough to justify the proposed restriction on the sale of this vitamin.

The Proposed Regulation Would be Largely Ineffective but Would be Economically Damaging to the Public

It is customary now for people who recognize improvement in their health with increased intake of vitamin A to purchase capsules containing 25,000 IU, at a retail price of about $5.00 for a year's supply (365 capsules).

If these capsules could not be obtained, many people probably would take five 5,000 IU capsules per day. The regulation would be ineffective, but it would have some nuisance value in discouraging some people from improving their health by reaching the optimum intake of this vitamin.

Inspection of price lists shows that the cost per unit of vitamin capsules containing 5000 or 10,000 IU is two or three times that of capsules containing 25,000 IU. Accordingly the proposed regulation, if put into effect, would mean for many people only an unnecessary extra cost of $5.00 or $10.00 per year paid for this important nutrient.

A fraction (rather small) of the American people might rely upon their physicians to prescribe vitamin A for them. They also would suffer financially, in having to pay the physician for writing the prescription and in having to pay the customary overcharge for prescriptions as compared with over-the-counter items.

The Proposed Action Would Limit the Freedom of the People

The proposed restriction on the sale of vitamin A would, if it went into effect, limit the freedom of the American people, with no discernible advantage to the country or the government, and with disadvantage to the people themselves. It probably would lead to a black market in vitamin A capsules, and to the increase in crime that is associated with the development of a black market. The Volstead Act, which limited the sale of alcoholic liquors except on a physician's prescription, had some justification, but it failed. The proposed limitation of the sale of vitamin A has no justification.

For the reasons given above, this proposed regulation should be rejected.

Linus Pauling

COPY

Department of Health, Education and Welfare
Room 6-88
5600 Fishers Lane
Rockville, Md. 20852

Comments concerning proposed policy statement concerning Vitamin A and vitamin D.

Although an employee of the Food and Drug Administration, Division of Nutrition for over twenty two years I have been informed that there is no reason that I cannot respond as an interested party.

Several years of my professional life with FDA was spent as an analyst, both biological and chemical, of the vitamins A and D. Also I have spent some time with research involving actions of both vitamins and as a result of this work and a literature search performed for the part 125, Special Dietary Food Hearings, I am reasonably acquainted with the scientific literature involving these two vitamins.

My objection is not to the general need to limit the availability of products that will supply truly dangerous amounts of them but to the levels chosen. In truth, the only thing that the proposed policy will accomplish is a form of harassment to the individuals who choose to take high levels of either. This may be somewhat effective in that it doubles or quadruples the number of pills but usually for these individuals the quantity is no deterant however it does increase the cost.

I have no strong objection to the 10,000 unit limit for vitamin A but since this level or even a somewhat higher level is not really dangerous I feel that a prescription requirement is rather capricious and highly subjective. I would suggest that potencies between 8,000 (the allowance for pregnancy) and 15,000 be designated as OTC drugs. Since this would be beyond the allowable potency for a dietary supplement and below a potency required for therapeutic use, this range is effectively eliminated since adequate directions for use cannot be written unless future research demonstrates an effective therapeutic use in this range. For the sake of uniformity the Canadian floor of 10,000 could be used for the OTC range but the supplement level should then be raised to this level, at least for use in products intended for use in pregnancy and lactation, since there really are no demonstrated hazards up to this level. Products for adult use could be properly and reasonably limited to 7,500 units, 150% of the adult RDA.

The 400 unit limit for vitamin D is most unreasonable, ill conceived and irrational. This tight limit at the RDA implies a very narrow and critical

PROPOSED STATEMENT OF POLICY

limit for toxicity which is not true. I agree that there are no normal circumstances when consumption of more than the 400 units is of value, especially for the adult, but the available information does not justify as reasonable the establishment of a requirement of a prescription for this level. It is most irrational because, as a matter of fact, because of analytical difficulties and manufacturing practices, there is not a 400 unit product on the market that does not actually contain an excess which in spite of labeling would catagorize it as a prescription product. In addition, many natural sources of A and D contain them in a ratio of 10:1 which would force manufacturers using them to underclare the vitamin D in order to comply with the limit. This would be contrary to the purpose of the policy and in addition results in an FDA inforced mislabeling which is most certainly contrary to the intent of the whole FD & C law. It has also come to my attention that some purveyors of natural vitamin A simply do not label any vitamin D, probably because of the difficulty and expence of the assay and quality control but it may also be deliberate because of a rather general feeling on the part of potential consumers that excess vitamin D is not desirable. This whole area is inconsistant with the false but implied danger of vitamin D levels above 400 units in this proposal. I would suggest adoption of the Canadian 1,000 unit limit with the range between 600 (150% of the RDA) and 1,000 units as OTC. Difficulties with."directions for use", as for vitamin A, would also apply to this range.

Sincerely yours,

Glen M. Shue

Glen M. Shue
Technical Assistant
Division of Nutrition
Food and Drug Administration

17 January 1973

AMERICAN MEDICAL ASSOCIATION

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COUNCIL ON
FOODS AND NUTRITION

Office of the Secretary

February 13, 1973

Miss Beryl McCullar
Hearing Clerk
Department of Health, Education,
and Welfare
Room 6-88
5600 Fishers Lane
Rockville, Maryland 20852

Dear Miss McCullar:

The Council on Foods and Nutrition has reviewed the Proposed Statement of Policy on Vitamin A and Vitamin D published in the Federal Register of December 14, 1972 (37CFR 26618).

The Council endorses the proposal to restrict the amounts of vitamin A and vitamin D in over-the-counter preparations.

Evidence for the restriction of vitamin D beyond that given in the preamble to the proposed amendment, may be found in a paper by Alan I. Fleischman, et al, "Vitamin D and Hypercholesterolemia in Adult Humans," pp. 468-472 in "Atherosclerosis: Proceedings of the Second International Symposium"; Springer-Verlag, New York-Heidelberg-Berlin, 1970. The studies reported significant increase in plasma cholesterol with the ingestion of 1,000 IU vitamin D daily.

The Council also notes that the discussion of the NAS/NRC RDA in the December 14 proposal fails to mention that there is no RDA for vitamin D in the case of adults. Requirements are presumably met by ordinary mixed diets and exposure of the skin to sunlight.

The Council assumes that the establishment of finite upper limits for vitamins A and D, would not preclude controlled "overage" to assure compliance with label declarations of the amounts present.

The maximum amount of vitamin A, 10,000 IU, that would be permitted by the present proposal is greater than the maximum permitted in the proposal published in the January 19, 1973 Federal Register, namely 5,000 IU for adults and 8,000 IU for pregnant or lactating women (38CFR2161-2162).

Recognizing that the present proposal is of an interim nature to place limits on over-the-counter preparations, the Council endorses the upper limit of 10,000 IU of vitamin A. The Council on Foods and Nutrition will comment at a later date on the proposals of January 19, 1973.

Sincerely,

Philip L. White

Philip L. White, Sc.D.
Secretary

PLW:vm
enclosures: 4 copies of this letter of February 13, 1973

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194a

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February 15, 1973

Miss Beryl McCullar, Hearing Clerk
Department of Health, Education
and Welfare
Room 6-62
5600 Fishers Lane
Rockville, Maryland 20852

Dear Miss McCullar:

The Committee on Nutrition of the American Academy of Pediatrics, which has been active in nutritional matter for over 15 years, wishes to comment on the proposed regulations concerning Vitamin A & D which appeared in the Federal Register, Vol. 37, No. 241, December 14, 1972, pages 26618-26620.

The Committee on Nutrition recommends that Vitamin D in amounts up to 1000 I..U. be allowed without prescription in foods for ~~special dietary~~ use for specific medical problems - in this instance foods, designed for dietary management of subjects with poor Vitamin D absorption and steatorrhea or fat malabsorption.

Considerable evidence exists that there is Vitamin D deficiency leading to osteomalacia associated with steatorrhea. Providing Vitamin D in amounts up to 1000 I.U. for daily consumption in foods designed for patients with steatorrhea will provide some protection from Vitamin D deficiency and entails no risk of Vitamin D excess. This exception is requested only for special foods and not for vitamin and mineral ~~supplements because~~ the latter may be used in excess, whereas the foods cannot be taken in great excess.

This exception will permit continued use of established recommended dietary regimens for steatorrhea. Your consideration of this proposal will be appreciated.

Very sincerely yours,

Malcolm A. Holliday

Malcolm A. Holliday, M.D.
Chairman, Committee on Nutrition
American Academy of Pediatrics

MAH:vs

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Oklahoma State University
Department of Food, Nutrition and Institution Administration
STILLWATER, OKLAHOMA 74074
(405) 372-6211, Exts. 6007, 6091

April 16, 1973

Federal Register
Hearing Clerk
Department of Health, Education, and Welfare
Food and Drug Administration
Washington, D.C. 20000

The Oklahoma Nutrition Task Force wishes to state that we are in accord with the proposal to limit the strength of Vitamin A adn D products available for over-the-counter sale. The proposed daily limit of 10,000 I.U. for Vitamin A and 400 I.U. for Vitamin D is at a level assumed to be within safe limits. Evidence of fat soluble vitamin toxicities has been established and high dosages pose health hazards.

We concur that these products should be regulated for consumer protection as long as non-prescription vitamin supplements are freely available.

Esther Winterfeldt

Esther Winterfeldt, Ph.D.
Chairman
Oklahoma Nutrition Task Force

EW:bw

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196a

January 22, 1973

Miss Beryl McCullar, Hearing Clerk
Department of Health, Education and Welfare
Room 6-62
5600 Fishers Lane
Rockville, Maryland 20852

Dear Miss McCullar:

1. I fully support the proposal (FDA, December 14, 1972) requiring all preparations providing daily dosage of more than 10,000 I. U. vitamin A or 400 I. U. vitamin D to be sold by prescription only.

2. The objections raised by pharmaceutical houses are based on the argument that this regulation will inconvenience certain patients with malabsorption and will stifle development of special foods. Both arguments are fallacious.

The drug houses have long used "special needs" as a front for promoting useless and dangerous nutrient remedies, e.g. artificial sweeteners, a nonsensical aid for diabetics, was promoted into a national industry.

Persons with special dietary needs would be better served by prescription nutrients. Indeed, I think all vitamin preparations should be put on prescription requirement, and I think this will happen in time. The A/D requirement is a good beginning. In my opinion, a maximum of 5,000 I. U. for vitamin A would have been more judicious. I hope that the OTC Drug Advisory Review Panel will consider this proposal.

Sincerely yours,

George V. Mann

George V. Mann, M.D.
Vanderbilt University

GVM:jv

The United Liverpool Hospitals 197e

Department of Chemical Pathology, Ashton Street, Liverpool L3 5RT.

Telephone: 051-709 2085

If telephoning, please ask for

Your ref:

Our ref: WHT/JIC

2nd January, 1973

The Hearing Clerk,
Department of Health, Education and Welfare,
Rm. 6-88,
5600 Fisher's Lane,
Rockville, Maryland 20852,
U.S.A.

Dear Sir,

I understand from Dr. J. Yogamundi Moon that the Food and Drug Administration is, at present, considering a proposal to make all preparations containing over 400 I.U. of vitamin D available only on a prescription. Dr. Moon has suggested that I might send to you a copy of my recent paper on the relationship between renal calculi and self-medication with multivitamin preparations. I have pleasure in enclosing this paper.

Since the publication of this paper we have accumulated further evidence, as yet unpublished, that the continued administration of amounts of vitamin D of the order of 500 to 1,500 I.U. daily over several months promotes a hypercalciuria in a proportion of subjects. We have also found from studies of dietary history that very few normal, healthy adults take, or appear to need, more than 200 I.U. of vitamin D daily and the mean value is closer to 100 I.U. daily.

From these facts, and from those already published in the enclosed paper, I would like to suggest to the F.D.A. that:

1. All preparations should contain an exact amount of vitamin D and not, as is so often the case, a minimal amount. This latter practice may lead to very considerably more vitamin D being taken than is intended.

2. The preparations containing vitamin D should be of two sorts:

    a. Those which can be purchased from pharmacists without prescriptions. For these I recommend that each tablet or capsule should contain 100 I.U. of vitamin D, and that the recommended dose should not exceed one tablet or capsule daily.

b. Preparations containing greater than 100 I.U. per tablet or capsule should be available only on a prescription and should be used for the treatment of established deficiency disorders, such as malabsorption, senile osteomalacia and so forth.

I would regard 100 I.U. daily (as in 2a.) as being a perfectly adequate supplement for any normal adult. I would regard the safety margin as being slight, so that 400 I.U. daily, if combined with a diet rich in foods containing natural or added vitamin D, could place a normal adult at risk of hypercalciuria and then of renal stone formation.

I would be very pleased to discuss this matter more fully if anybody in the organisation would wish me to do so.

I hope that my writing to you in this way is in order; it is not in any way intended to be presumptuous.

Yours faithfully,

W. H. Taylor

W. H. Taylor, M.A., B.Ch., D.M.(OXON).
F.R.C.P.
Consultant Chemical Pathologist,
Director of Studies in Chemical Pathology,
University of Liverpool.

Clinical Science (1972) 42, 515–522.

RENAL CALCULI AND SELF-MEDICATION WITH MULTIVITAMIN PREPARATIONS CONTAINING VITAMIN D

W. H. TAYLOR

Department of Chemical Pathology, The United Liverpool Hospitals

(*Received* 10 *December* 1971)

SUMMARY

1. Of 104 patients with renal calculi, 42% gave a history of previous self-medication with multivitamin preparations containing vitamin D, compared with 37% of a control group of fifty-one patients without renal calculi. This difference is not significant.

2. The mean supplemental daily intake of vitamin D and the annual intake were significantly higher in the patients with renal calculi than in the control group.

3. The highest mean supplemental intake of vitamin D occurred among those patients in whom no metabolic or other cause for renal stone formation could be found.

4. The first calculi presented within 2 years of the period of self-medication in twenty-four of thirty patients who had not previously suffered from renal stones.

5. The results suggest that self-administration of vitamin D should be included among the aetiological factors promoting the formation of renal calculi.

Key words: renal calculi, vitamin D, self medication.

In about one-third of the patients who are investigated for renal calculi, no metabolic or other cause can be found (Table 1), despite an exhaustive search for the known aetiological factors. The management of this group of patients is thus unsatisfactory, for without a known cause rational therapy is difficult.

A possible clue to the origin of renal calculi in some of these patients emerged while recording their dietary habits and supplemental vitamin D intake. It was observed that self-administration of vitamin D was quite common. The question is thus raised whether such self-administration makes a significant aetiological contribution to stone formation in this group of patients, and whether it perhaps aggravates the formation of calculi in other patients who have a known metabolic cause, such as idiopathic hypercalciuria.

The first step in investigating these possibilities seemed to be a statistical enquiry, the

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results of which suggest that vitamin D should now be included among the aetiological factors promoting the formation of renal calculi.

PATIENTS AND METHODS

The supplemental vitamin D intake of patients with renal calculi arising from different causes has been compared with that of a continuous series of fifty-one outpatients suffering from metabolic disorders without renal calculi (Table 1). The group with 'other metabolic causes'

TABLE 1. Self-administration of supplemental vitamin D in 104 patients with renal calculi compared with fifty-one out-patients with metabolic disease but without renal calculi

	No. of patients	Self-administration of preparations containing vitamin D, within previous:									
		16 years		10 years		5 years		2 years		1 year	
		No.	%	No.	%	No.	%	No.	%	No.	%
Patients without renal calculi	51	19	37	16	31	12	24	10	20	7	14
Patients with renal calculi associated with:											
Idiopathic hypercalciuria	46	18	39	17	37	13	28	10	22	9	20
Chronic urinary tract infection	12	6	50	6	50	4	33	4	33	3	25
Other metabolic causes	14	6	43	3	21	2	14	2	14	2	14
No known cause	32	14	44	14	44	13	41	7	22	5	16
Total	104	44	42	40	38	32	31	23	22	19	18

comprised six patients with idiopathic phosphaturia, seven with urate calculi and increased serum urate concentrations, and one with hyperoxaluria. The group with 'no known cause' consisted of patients in whom infection, primary hyperparathyroidism, idiopathic or other hypercalciuria, cystinuria, and the metabolic causes mentioned above had been excluded on one or more occasions. The age and sex composition of the groups of patients with and without renal calculi did not differ significantly.

The supplemental intake of vitamin D in the control patients and in all but four of those with renal calculi was ascertained by the same observer. The patients with renal calculi were referred from medical sources with either a confirmed diagnosis or with a history of apparent renal colic. The diagnosis was known at the first interview in only 38% of the control group. In both groups the information about vitamin D intake was obtained by using the same careful pattern of questioning, which came immediately after questions about the dietary history. The patient was asked if he or she had ever taken medicines for indigestion and, if so, their names; the possible intake of sodium bicarbonate was then specifically mentioned. The patient was next asked if at any period of his life he had taken other medicines or tablets obtained from pharmacists, and then, in particular, any containing extra vitamins. If the answer was

no, the patient was asked if vitamin tablets had ever been supplied by his employer(s), and if, specifically, he had ever taken vitamin D. If the answer was still no, the names of the most commonly used vitamin supplements were mentioned.

When the answer was yes, an attempt was made to establish the years of intake, the daily dosage and the duration of each period of continuous administration. It was possible to establish the years of intake by relating self-administration to specific events in the patient's life, and particularly to the onset of illness.

It was surprising to find that some patients gave quite clear and precise descriptions of supplemental vitamin D intake between 10 and 16 years previously. Because renal calculi may remain undetected for several years it was felt that such descriptions had relevance, despite any loss of accuracy caused by the passage of time, and they have therefore been included in the Tables.

The daily dosage was established by detailed questioning, particularly about the times of day at which the supplements were usually taken, and verified whenever possible by independent questioning of husbands or wives. The duration of continuous administration was cross-checked by asking how frequently bottles of tablets or capsules were purchased, and by ascertaining how many tablets or capsules were dispensed in each pack. The brand of supplement was checked by asking patients to describe the size, colour and shape. Finally the quantitative amounts of supplemental vitamin D were calculated from the vitamin D content of the tablets or capsules as quoted in the appropriate edition of the Extra Pharmacopoeia. No quantitative assessment of the information obtained in this enquiry was made, nor were any calculations made, until the enquiry had been completed.

RESULTS

Table 1 shows that the proportion of patients with renal calculi who said they had taken supplemental vitamin D, other than from their own doctor, at any time during the previous 16 years was greater than in the control group, but the differences are not significant. Vitamin supplements taken during childhood are excluded from the results.

Table 2 shows, however, that the mean additional daily intake of vitamin D during the period of supplementation was higher than in the control group in all but one of the groups with renal calculi. The mean intake for all the patients with renal calculi ($0{\cdot}04<P<0{\cdot}05$) and that for the group with 'no known cause' ($0{\cdot}02<P<0{\cdot}03$) both differed significantly from the mean intake of the control group. In other individual groups the difference was not statistically significant. It was also possible in most patients to assess the quantity of vitamin D taken in a year and Table 2 shows that significantly more patients with renal calculi ingested over 100 000 i.u. than in the control group ($P<0{\cdot}02$). The highest daily intake was 3600 i.u. and the highest yearly intake, 550 000 i.u.; both patients were in the group with 'no known cause' for their renal calculi.

Of the nineteen control patients who took supplementary vitamin D only five (26·3%) did so for more than 1 year. In contrast with this ten (55·6%) of eighteen patients with idiopathic hypercalciuria took vitamin D for more than 1 year, as did eighteen (41%) out of the total of forty-four patients with renal calculi. These differences are not statistically significant.

The time relationship between the appearance of the first renal calculus and the first

TABLE 2. Intake of vitamin D in those patients with renal calculi who had taken supplemental vitamin D, compared with that of patients without renal calculi

	Mean daily supplemental dosage (i.u.)	Daily supplemental vitamin D intake of individual patients (i.u.)						Supplemental intake of vitamin D in individual patients during 1 year	
		1–400	401–800	801–1200	1201–1600	1601–2000	>2000	Below 100 000 i.u.	Above 100 000 i.u.
Patients without renal calculi	691	8	7	2	0	2	0	16	3
Patients with renal calculi	982								
Those with:									
Idiopathic hypercalciuria	934	2	8	6	0	2	0	9	8
Chronic urinary tract infection	862	2	3	0	0	1	0	4	2
Other metabolic causes	630	2	3	1	0	0	0	3	3
No known cause	1254	3	5	2	1	2	1	6	8
Total		9	19	9	1	5	1	22	21

supplemental vitamin D is shown in Table 3. In fourteen patients the first renal calculus preceded the taking of vitamin D supplements, but within 2 years of taking the supplements six of these patients experienced further formation of renal calculi. In twenty-four patients the first evidence of renal calculus formation followed within 2 years of ingesting the additional vitamin D. In some patients there was more than one such related episode. For example, a 45-year-old male took 1650 i.u. of vitamin D daily, with a total dosage of 148 500 i.u. in 1962. His first renal calculus was passed in 1963. In 1964 and again in 1965 he took 1100 i.u.

TABLE 3. Appearance of symptoms or signs of renal calculi in relation to supplemental vitamin D intake

Patients with renal calculi associated with:	Calculi preceded supplements	Supplements preceded calculi by:		
		1 year	2 years	>2 years
Idiopathic hypercalciuria	8	6	3	1
Chronic urinary tract infection	0	3	2	1
Other metabolic causes	1	1	1	3
No known cause	5	6	2	1
Total	14	16	8	6

daily for 1 month. Two new renal calcuii were passed in 1966. If the intake of supplemental vitamin D were completely unrelated to the formation of renal calculi, it would be expected that the time-intervals between the two events would be more widely dispersed than was found (Table 3).

The proportion of patients whose stones developed after vitamin D ingestion (thirty of forty-four) is in fact significantly greater ($P<0{\cdot}05$) than that of patients who took vitamin D after first developing renal calculi (fourteen of forty-four). The assumption behind such a calculation would be that if the intake of vitamin D and the formation of renal calculi were unrelated, there would be equal chances of either event preceding the other in the patients who experienced both. It is impossible to prove or disprove such an assumption, so that the statistical difference is not one upon which reliance should be placed.

Patients and controls usually obtained their supplements by direct purchase from pharmacists. In only five instances were the preparations supplied by employers. Two preparations that have been particularly promoted by advertisement were consumed by about half of the patients and controls, thirty-one out of a total of sixty-three. These preparations are unfortunately among those which have the highest content of vitamin D per tablet or capsule; in both the quantity exceeds 500 i.u.

DISCUSSION

Patients' recollections of past events are notoriously subject to error. This error can be minimized, as in the present study, by adopting a standard manner of questioning, and by questioning a control group of patients in an identical fashion. The patients presented in such a way that the diagnosis of renal calculus was known or could be inferred. The metabolic

cause of the renal calculi was, however, not known in any patient at the time of questioning. Whereas possible subconscious bias cannot be fully eliminated, it is apparent from Table 2 that bias in questioning did not arise within, for example, the groups with 'other metabolic causes' or 'chronic urinary tract infection'. These results suggest that significant overall bias is unlikely to have occurred. Another possible source of error is that the tablets or capsules taken by the patients may not have contained the precise amounts of calciferol that are stated in the Extra Pharmacopoeia. This potential error is, however, approximately the same for the patients and the controls, for of the three most commonly used supplements, one was used by 20% of patients and 30% of controls, a second by 33% of patients and 20% of controls and a third by 18% of patients and 30% of controls. Thus three preparations accounted for 71% and 80% respectively of the supplements that were taken.

Although the questioning did not reveal any increasing uncertainty about vitamin D intake with passage of time, it is only reasonable to imagine that information recalled after, say, 10 years might not be very accurate. The bearing of these values on the observed differences can be assessed as follows. Three control patients gave information relating to the 10–16 year period and reported that their daily intakes were 250, 550 and 1800 i.u. If they were to be excluded, the control group mean and range would both be decreased. Four patients with renal calculi also gave information relating to the same period and reported daily intakes of 250, 550, 600 and 750 i.u. Since all these values are below the mean daily intake of this group (Table 2), their exclusion would raise the mean. Thus excluding all seven patients would enhance the significance of the difference (P now 0·03–0·04) between the respective means.

It was unexpected that as many as 37% of the patients without renal calculi were found to have taken vitamin D containing supplements, at their own expense, at some point within the previous 16 years. Questioning revealed that a few had undoubtedly been influenced by the various prophylactic claims made for the supplements, but many had felt generally unwell before their metabolic illness had become sufficiently severe to cause them to consult their family doctor, and they had hopefully tried, for a short time, the effect of a vitamin supplement at this early stage.

By contrast, the patients with renal calculi did not, in general, begin to take supplemental vitamins because they were feeling ill, as did the typical control patient, but because they wished to maintain a state of positive health and particularly to prevent winter colds. They thus took the vitamin supplements more regularly and often for longer periods. Those who considered the supplements to be effective naturally took them in subsequent years and sometimes in increased doses.

The differences between the control patients and those with renal calculi all point in the same direction, but only three have statistical significance. The mean daily supplemental intake of vitamin D was significantly higher in the patients with renal calculi than in the control group, and so was the ascertainable annual intake. The mean daily intake of the patients with 'no known cause' for the renal calculi was also significantly higher than that of the control group.

The question therefore arises as to whether the vitamin D supplements have contributed to the formation of renal calculi. Clearly the majority (58%) of patients with renal calculi had not taken extra vitamin D. On the other hand, the presentation of the disease in twenty-four of thirty patients within 2 years of taking the supplements points to the probability that the supplements were a contributing or precipitating factor, as does the fact that of the

fourteen patients who were known to have had renal calculi before ingesting vitamin D, six suffered further renal calculi within 2 years of the supplementation.

One possible mechanism by which the supplements could affect renal stone formation would be by increasing the absorption of dietary calcium and in turn the urinary excretion of calcium. It is, however, not certain that the amounts of vitamin D involved would promote a significant hypercalciuria. The experimental observations on this point are scanty and equivocal. McCance & Widdowson (1942) gave 2000 i.u. of vitamin D daily for 21 days to four normal men and four normal women. They found no increase of urinary calcium output and were thus in agreement with previous observations, which they cited, but of which they were justifiably critical. Their studies are not precisely related to ours, because our patients took their vitamin supplements for a longer time. It is curious, too, that in their eight subjects the daily urinary calcium output ranged from 27 to 179 mg, with five values of 100 mg or less. In contemporary practice, values below 100 mg would be considered low and worthy of further investigation. Flocks (1940) found that, 'in ordinary therapeutic dose in the normal individual, vitamin D raises the urinary calcium not more than 50 mg per 24 hours'. Unfortunately the dosage of vitamin D and the time for which it was given are not stated. He makes the further interesting observation that, 'individuals with so-called "idiopathic" increased urinary calcium show marked response to vitamin D intake', and quotes a range for urinary calcium of 300–500 mg daily, that increases with vitamin D administration (amount not stated) to 500–750 mg daily. Knapp (1947) gave boys aged 1–12 years 340 i.u. of vitamin D daily and found an increased urinary calcium output, but this did not happen in girls treated similarly.

Ideally one would like to know just how sensitive the urinary calcium output is to long-term supplements of vitamin D in patients with renal calculi and in controls, but in the former group at any rate, in the light of the evidence presented in Tables 1–3, such an investigation would scarcely be ethically justifiable. The writer has, however, observed personally that many patients who absorb calcium poorly (for a variety of reasons) and who have been maintained for some weeks in neutral balance on supplements of vitamin D of the order of 500–3000 i.u. daily, often develop hypercalciuria and then require a reduction in their maintenance dose. It would thus not be incompatible with the available evidence to postulate that long-continued supplementary vitamin D in patients without malabsorption eventually increases the absorption of calcium to a point that promotes a hypercalciuria, which in turn would favour increased deposition of calcium in the kidneys. Clearly, patients who normally have above normal calcium intakes would be especially at risk, as would patients who already have idiopathic hypercalciuria [particularly if, as Flocks (1940) suggests, they are unduly sensitive to vitamin D] or some other cause of renal stone formation.

An unexpected finding of this investigation has been the previous relatively high intake of vitamin D in many of the patients with 'no known cause' for their renal calculi. If this supplementation has contributed to the formation of renal calculi, then the group of subjects with 'no known cause' has been decreased further, so that a group of only about 20% remains without even a partial explanation of their renal calculi.

The preparations that were taken also contained vitamin A, except for one, which was taken by one patient in each of the two groups. Similar differences between the groups are likely therefore to exist for vitamin A intake as for vitamin D, but from the known actions of the two vitamins, it seems more probable that formation of renal calculi is related to the latter than to the former. Other vitamins were contained in the preparations taken in 70%

of the control patients and in 57% of these with renal calculi. Similar differences between the groups are thus less likely than with vitamin A, and again the actions of other vitamins are not known to be related to renal stone formation. Two of the control patients had taken medicaments containing small amounts of calcium, as had three of the patients with renal calculi. These supplements are unlikely to affect the validity of the conclusions.

If it is accepted that there is an association between self-supplementation with vitamin D and the formation of renal calculi, the amounts of vitamin D in multivitamin preparations may need to be modified. In the report of the Department of Health and Social Security (1969) it is said of vitamin D that 'of the requirements of adults, including the elderly, practically nothing is known', and a daily adult intake of 100 i.u. is recommended 'as a safety measure'. Over the last two decades there has been a general recognition that in groups thought to be particularly vulnerable to vitamin D deficiency, such as young children, pregnant women and lactating mothers, the recommended intake of vitamin D should be decreased (Department of Health and Social Security, 1969). A reappraisal of adult supplements may therefore be appropriate. Of twenty-six proprietary multivitamin tablets or capsules listed in the Extra Pharmacopoeia (1967), only three contain less than 300 i.u. whereas fourteen contain 500 i.u. or more and three contain 1000 i.u. If patients are able to obtain multivitamin supplements without prescription there seems to be no good reason for a tablet or capsule to contain more than the recommended daily adult intake.

Therefore the following are suggested. (a) Patients who have suffered from renal calculi should avoid self-medication with vitamin supplements containing vitamin D. (b) When vitamin tablets are prescribed for patients who are eating food normally and who do not suffer from malabsorption, the daily supplemental intake of vitamin D should not exceed the recommended daily adult intake. (c) A distinction should be made, with respect to the content of vitamin D, between multivitamin preparations that are meant to be used to maintain an optimum normal intake of nutrients and those that are intended to combat deficiencies, as in the various malabsorption syndromes. It would be desirable for the latter preparations to be available only on medical prescription.

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EXCERPTS FROM UNITED STATES PHARMACOPEIA, NATIONAL FORMULARY AND FOOD AND NUTRITION BOARD, PUBLICATION

when there is a breakdown in homeostatic mechanisms or when the load of sodium presented to the body, or the losses issuing therefrom, exceeds the coping abilities of these mechanisms. Abnormal losses occur as a result of diarrhea and vomiting, in chronic renal disease, in adrenal insufficiency, and following the prolonged use of diuretics. Sweat contains 20 to 50 meq of sodium per liter, so that excessive sweating can lead to losses of as much as 350 meq of sodium per day. Whenever more than 4 liters of water are consumed, extra sodium chloride should be provided—approximately 17 mM (1 g) per liter of extra water. In unadapted individuals, the need for additional water may be somewhat higher. Sodium concentrations in sweat are high (50 to 150 meq/liter) in patients with cystic fibrosis of the pancreas.[5]

Diets restricted in sodium are used in the treatment of a number of conditions, notably those involving cardiac failure and edema formation. Since prolonged feeding of high-salt diets to experimental animals leads to hypertension, the possibility that excessive intakes could be of etiologic significance in human hypertensive disease is of current interest.

Potassium also is widely distributed in foods, the usual intake being 50 to 150 meq/day.[6] Potassium deficiency is a well-defined syndrome that complicates many pathologic states. Care should be used to ensure an adequate intake of potassium during prolonged intravenous feeding, during recovery from severe diarrhea or diabetic acidosis, and in patients given diuretics. An intake of 1 to 3 meq/kg/day should be sufficient for this purpose. High levels of serum potassium also lead to toxicity, principally manifested by cardiac conduction defects and cardiac failure, so it is imperative to curtail drastically or even eliminate dietary potassium in patients with advanced renal failure.

Chloride is the most important anion in the maintenance of fluid and electrolyte balance.[7,8] The daily turnover in adults (intake-output) ranges between 85 and 250 meq.

WATER

Water is the most abundant body constituent, accounting for 1/2 to 3/4 (depending on age and body fat) of the body weight. It is the milieu for all chemical processes. Deficits or excesses of more than a few percent are incompatible with health.[1] The normal rate of turn-

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Assay—Using a suitable quantity of Vitamin A, accurately weighed, proceed as directed under *Vitamin A Assay*, page 914.
Packaging and storage—Preserve in tight containers, preferably under an atmosphere of an inert gas, protected from light.
Labeling—Label it to indicate the form in which the vitamin is present, and to indicate the presence of any antimicrobial agent, dispersant, antioxidant, or other added substance, and to indicate the vitamin A activity in terms of the equivalent amount of retinol, in mg. per g., and in U. S. P. Vitamin A Units.*

CATEGORY: Anti-xerophthalmic vitamin; also see *Decavitamin Capsules* and *Tablets*.

USUAL DOSE: Prophylactic, 1.5 mg. (5000 U. S. P. Vitamin A Units) once a day.
Therapeutic, 7.5 mg. (25,000 Units) once a day.

USUAL DOSE RANGE: Prophylactic, 1.2 to 2.4 mg. (4000 to 8000 Units) daily.
Therapeutic, 7.5 to 60 mg. (25,000 to 200,000 Units) daily.

Vitamin A Capsules

Vitamin A Capsules contain not less than 95.0 percent of the labeled amount of vitamin A.

Weight variation, page 950: meet the requirements for *Capsules*.
Other requirements—The contents of Capsules respond to the *Identification tests* and meet the requirements of the test for *Absorbance ratio* under *Vitamin A*, page 775.
Assay—Using not less than 5 Vitamin A Capsules, proceed as directed under *Vitamin A Assay*, page 914. Calculate the content of retinol ($C_{20}H_{30}O$) in mg. and in U. S. P. Vitamin A Units per Capsule.
Packaging and storage—Preserve in tight, light-resistant containers.
Labeling—Label Capsules to indicate the form in which the vitamin is present, and to indicate the vitamin A activity in terms of the equivalent amount of retinol in mg. and in U. S. P. Vitamin A Units per Capsule.
Capsules available—Capsules usually available contain the following amounts of vitamin A: 1.5, 7.5, 15, and 30 mg. (5000, 25,000, 50,000, and 100,000 U. S. P. Vitamin A Units).

CATEGORY and DOSE: See *Vitamin A*.

Warfarin, Sodium *page 675*
Warfarin, Sodium, for Injection *page 676*
Warfarin, Sodium, Tablets *page 677*

Water

H_2O 18.02

Description: Clear, colorless, odorless liquid.

* *Note*—One U. S. P. Vitamin A Unit is the specific biologic activity of 0.3 mcg. of the all-trans isomer of retinol.

Reaction—[NOTE—For this test, use indicator test solutions specified for pH determinations (see under *Test Solutions* in the section, *Reagents, Indicators, and Solutions*, page 952).] Add 2 drops of methyl red T.S. to 10 ml. of Water in a test tube: no pink or red color is produced. To another 10-ml. portion of Water in a test tube add 2 drops of phenolphthalein T.S.: no pink or red color is produced.

Heavy metals—Adjust 40 ml. of Water with diluted acetic acid to a pH of 3.0 to 4.0 (using short-range pH indicator paper), add 10 ml. of freshly prepared hydrogen sulfide T.S., and allow the liquid to stand for 10 minutes: the color of the liquid, when viewed downward over a white surface, is not darker than the color of a mixture of 40 ml. of the same Water with the same amount of diluted acetic acid as was added to the sample and 10 ml. of Purified Water (see page 779), matched color-comparison tubes being used for the comparison.

Zinc—To 50 ml. contained in a test tube add 3 drops of glacial acetic acid and 0.5 ml. of potassium ferrocyanide T.S.: the solution shows no more turbidity than that produced by 50 ml. of purified water in a similar test tube, treated in the same manner, and viewed downward over a dark surface.

Foreign volatile matter—When heated nearly to the boiling point and agitated, it evolves no odor.

Total solids—Evaporate 100 ml. on a steam bath to dryness, and dry the residue at 105° for 1 hour: not more than 100 mg. of residue remains (0.1 percent).

Bacteriological purity—It meets the United States Public Health Service regulations for potable water with respect to bacteriological purity.

CATEGORY: Pharmaceutic aid (solvent).

Water for Injection

Water for Injection is water purified by distillation. It contains no added substance.

Caution—Water for Injection is intended for use as a solvent for the preparation of parenteral solutions. For parenteral solutions that are prepared under aseptic conditions and are not sterilized by appropriate filtration or in the final container, first render the Water for Injection sterile and thereafter protect it from microbial contamination.

Description: Clear, colorless, odorless liquid.

Pyrogen—When previously rendered isotonic by the addition of 600 mg. of pyrogen-free sodium chloride for each 100 ml., it meets the requirements of the *Pyrogen Test*, page 880.

Other requirements—It meets the requirements of the other tests under *Purified Water*, page 779, with the exception of the test for *Bacteriological purity*.

Packaging and storage—Preserve in tight containers. It may be stored at a temperature below or above the range in which microbial growth occurs.

CATEGORY: Pharmaceutic aid (solvent).

Bacteriostatic Water for Injection

Bacteriostatic Water for Injection is sterile water for injection containing one or more suitable antimicrobial agents.

Note—Use Bacteriostatic Water for Injection with due regard for the compatibility of the antimicrobial agent or agents it contains with the particular medicinal substance that is to be dissolved or diluted.

Acid value, page 905: not less than 196 and not more than 204, about 2 g., accurately weighed, being used.
Iodine value, page 905: not less than 85 and not more than 95.
Packaging and storage—Preserve in tight containers.

CATEGORY: Pharmaceutic aid (solvent).

Olive Oil

Olive Oil is the fixed oil obtained from the ripe fruit of *Olea europæa* Linné (Fam. *Oleaceæ*).

Description: Pale yellow, or light greenish yellow, oily liquid, having a slight, characteristic odor and taste, with a faintly acrid aftertaste.
Solubility: Slightly soluble in alcohol. Miscible with ether, with chloroform, and with carbon disulfide.
Specific gravity, page 943: not less than 0.910 and not more than 0.915.
Heavy metals, *Method II*, page 897: 10 parts per million.
Cottonseed oil—Mix 5 ml. in a test tube with 5 ml. of a mixture of equal volumes of amyl alcohol and a 1 in 100 solution of sulfur in carbon disulfide, warm the mixture carefully to expel the carbon disulfide, and immerse the test tube to one-third of its length in a boiling, saturated solution of sodium chloride for 2 hours: the mixture develops no reddish color.
Peanut oil—Saponify 10 g. by heating for 1 hour under a reflux condenser with 80 ml. of alcoholic potassium hydroxide solution (1 in 20). Add phenolphthalein T.S., neutralize with diluted acetic acid, and wash the solution into 120 ml. of boiling lead acetate T.S. contained in a conical flask. Boil the mixture for 1 minute, and cool by immersing the flask in cold water, rotating the contents occasionally to cause the precipitate to adhere to the walls of the flask. Decant the liquid, wash the precipitate with cold water to remove the excess lead acetate, and then wash with 90 percent (by volume) alcohol. Add 100 ml. of ether, stopper the flask well, and allow to stand until the precipitate is disintegrated. Connect the flask to a reflux condenser, boil for 5 minutes, cool to about 15°, and allow to stand overnight. Filter, and thoroughly wash the precipitate with ether. With the use of a jet of ether, transfer the precipitate to a 500-ml. separator, alternating the jet of ether with diluted hydrochloric acid at the end if any of the precipitate adheres to the filter paper. Add sufficient diluted hydrochloric acid to make the total acid layer measure about 100 ml., and add sufficient ether to make the ether layer measure about 100 ml. Shake the mixture vigorously for several minutes, allow the layers to separate, draw off the acid layer, and wash the ether once by shaking with 50 ml. of diluted hydrochloric acid and finally with several portions of water until the last washing is not acid to methyl orange T.S. Transfer the ether solution to a dry flask, evaporate the ether, add a small amount of dehydrated alcohol, and evaporate on a steam bath to dryness. Dissolve the residue of dry fatty acids by warming with 60 ml. of 90 percent (by volume) alcohol, slowly cool the solution to 15° while shaking frequently, and allow the solution to stand at 15° for 30 minutes: no crystals separate from the solution.
Sesame oil—Mix 10 ml. with 10 ml. of hydrochloric acid, add 0.1 ml. of a 1 in 50 solution of furfural in alcohol, and shake the mixture vigorously for 15 seconds: no pink to crimson color appears in the acid layer when the emulsion breaks. If any color appears in the acid layer, add 10 ml. of water, and again shake the mixture vigorously: in the absence of sesame oil any pink color is evanescent.
Teaseed oil—In a dry, 18- × 150-mm. test tube place 0.8 ml. of acetic anhydride, 1.5 ml. of chloroform, and 0.2 ml. of sulfuric acid, mix, and cool in a water bath to 25°. Add about 200 mg. of Olive Oil (about 7 drops), mix, and cool to 25°. If the solution is cloudy, add acetic anhydride, dropwise, shaking after each addition, until the solution suddenly clears. Allow the mixture to remain in the water bath for 5 minutes: it shows a green color by both reflected and transmitted light. Add 10 ml. of absolute ether, and mix by inverting the tube: the initial green color fades to a brownish gray. (Before the dilution with ether, the presence of *linseed oil* will cause a brown color to appear by transmitted light, and after the dilution, a transient red color.)
Free fatty acids, page 903—The free fatty acids in 10 g. require for neutralization not more than 5 ml. of 0.1 *N* sodium hydroxide.
Iodine value, page 905: not less than 79 and not more than 88.

Solubility: Freely soluble in water, in saline T.S., and in dextrose solutions; insoluble in most organic solvents.
Other requirements—It complies with the pH, moisture content, specific rotation, potency, and other requirements of the F.D.A. concerning Sodium Cephalothin.
Packaging and storage—Preserve in tight containers.

CATEGORY: Antibacterial.
USUAL DOSE: Parenteral, the equivalent of 500 mg. to 1 gram of cephalothin four to six times a day.
USUAL DOSE RANGE: 2 to 8 grams daily.

Sterile Sodium Cephalothin

Sterile Sodium Cephalothin is sodium cephalothin suitable for parenteral use. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{16}H_{15}N_2NaO_6S_2$. It conforms to the regulations of the federal Food and Drug Administration concerning antibiotic drugs (see *Antibiotics*, page 791).

Other requirements—It conforms to the definition, *Description*, and *Solubility* statement under *Sodium Cephalothin*, page 614. It complies with the identification, pH, moisture content, specific rotation, pyrogen, sterility, potency, and other requirements of the F.D.A. concerning Sterile Sodium Cephalothin.
Packaging and storage—Preserve in *Containers for Sterile Solids*, as described under *Injections*, page 797.
Sizes available—It is usually available in the following amounts: 1 and 4 g.

CATEGORY and DOSE: See *Sodium Cephalothin*.

Sodium Chloride

NaCl 58.44

Sodium Chloride contains not less than 99.5 percent and not more than 100.5 percent of NaCl, calculated on the dried basis. It contains no added substance.

Description: Colorless, cubic crystals or white, crystalline powder. Has a saline taste.
Solubility: Freely soluble in water, and slightly more so in boiling water; soluble in glycerin; slightly soluble in alcohol.
Identification—A solution (1 in 20) responds to the tests for *Sodium*, page 893, and for *Chloride*, page 892.
Acidity or alkalinity—Dissolve 50 g. in 200 ml. of carbon dioxide-free water, and add 10 drops of bromothymol blue pH indicator. If the solution is yellow, it requires not more than 1.0 ml. of 0.02 *N* sodium hydroxide to produce a blue color. If the solution is blue or green, it requires not more than 2.0 ml. of 0.02 *N* hydrochloric acid to produce a yellow color.
Loss on drying, page 935—Dry it at 105° for 2 hours: it loses not more than 0.5 percent of its weight.
Iodide or bromide—Digest 2 g. of finely powdered Sodium Chloride for 3 hours with 25 ml. of warm alcohol, cool the mixture, and remove the undissolved salt by filtration. Evaporate the filtrate to dryness, dissolve the residue in 5 ml. of water, add 1 ml. of chloroform, and cautiously introduce, dropwise, with constant agitation, 5 drops of dilute chlorine T.S. (1 in 3): the chloroform does not acquire a violet, yellow, or orange color.

Calcium and magnesium—Dissolve 20 g. in 200 ml. of water, add 0.1 ml. of hydrochloric acid, 5 ml. of a pH 10 buffer solution, and 5 drops of eriochrome black T.S. Titrate with 0.05 *M* disodium ethylenediaminetetraacetate to a pure blue end-point. Each ml. of 0.05 *M* disodium ethylenediaminetetraacetate is equivalent to 2.004 mg. of Ca. Not more than 0.05 percent of calcium and magnesium (as Ca) is found.

Sulfate, page 885—A 6.25-g. portion shows no more sulfate than corresponds to 0.15 ml. of 0.02 *N* sulfuric acid (150 parts per million).

Sodium ferrocyanide—Dissolve 25 g. in 80 ml. of water in a glass-stoppered, 100-ml. graduated cylinder or flask. Add 2 ml. of ferrous sulfate T.S. and 1 ml. of diluted sulfuric acid, dilute with water to 100 ml., and mix. For a control, dissolve another 25 g. in 80 ml. of water, dilute with water to 100 ml., and mix. Transfer 50-ml. portions of the respective solutions to matched color-comparison tubes: the solution to which ferrous sulfate T.S. was added shows no blue color when compared with the control.

Assay—Weigh accurately about 250 mg. of Sodium Chloride, dissolve in 50 ml. of water in a glass-stoppered flask, and add 50.0 ml. of 0.1 *N* silver nitrate, 3 ml. of nitric acid, 5 ml. of nitrobenzene, and 2 ml. of ferric ammonium sulfate T.S. Shake well, and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 5.844 mg. of NaCl.

Packaging and storage—Preserve in well-closed containers.

CATEGORY: Electrolyte replenisher; also see *Dextrose and Sodium Chloride Injection*, *Mannitol and Sodium Chloride Injection*, *Ringer's Injection*, and *Lactated Ringer's Injection*.

USUAL DOSE: Oral, 1 gram three times a day.
Intravenous infusion, 1 liter of a 0.9 percent solution.
Topically to wounds and body cavities, as a 0.9 percent solution for irrigation.

USUAL DOSE RANGE: Oral, 3 to 6 grams daily.

Sodium Chloride Injection

Sodium Chloride Injection is a sterile, isotonic solution of sodium chloride in water for injection. It contains no antimicrobial agents. It contains not less than 0.85 percent and not more than 0.95 percent of NaCl.

Identification—It responds to the tests for *Sodium*, page 893, and for *Chloride*, page 892.

Pyrogen—It meets the requirements of the *Pyrogen Test*, page 886.

pH, page 938: between 4.5 and 7.0.

Arsenic, page 894—Use 35 ml. of Injection. The limit is 0.08 part per million.

Heavy metals, page 897—To 20 ml. of Injection add 2 ml. of diluted acetic acid, then dilute with water to 25 ml.: the heavy metals limit is 0.3 part per million.

Other requirements—It meets the requirements of the test for *Ferrocyanide* under *Dextrose and Sodium Chloride Injection*, page 181, except that 40 ml. of Injection is used, and it meets the requirements under *Injections*, page 797.

Assay—Pipet 25 ml. of Sodium Chloride Injection into a glass-stoppered flask, add 50 ml. of water, mix, and add 50.0 ml. of 0.1 *N* silver nitrate, 3 ml. of nitric acid, 5 ml. of nitrobenzene, and 2 ml. of ferric ammonium sulfate T.S. Shake well, and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 5.844 mg. of NaCl.

Packaging and storage—Preserve in single-dose containers, preferably of Type I or Type II glass.

Injections available—Injection is usually available in the following volumes: 100, 150, 250, 500, and 1000 ml.

CATEGORY: Fluid and electrolyte replenisher; irrigating solution.

USUAL DOSE: Intravenous infusion, 1 liter.
Topically to wounds and body cavities, for irrigation.

The Pharmacopeia of the United States of America

(*The United States Pharmacopeia*)

Eighteenth Revision

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radioisotopes it is therefore necessary to make the comparison of the spectrum with that of a known sample of the radionuclide obtained in the same instrument under identical conditions.

Radiation Shielding— Adequate shielding must be used to protect laboratory personnel from all ionizing radiation, and measuring instruments from background radiation.

Alpha and beta radiation is readily shielded because of its limited range of penetration. The range of alpha and beta particles varies inherently with their kinetic energy. The alpha particles are monoenergetic and have a range of a few centimeters in air. The absorption of beta particles, owing to their continuous energy spectrum and scattering, follows apparently an exponential function. The range of beta particles in air varies from centimeters to meters. Beta radiation produces an undesirable secondary radiation upon absorption by shielding materials. This radiation, known as Bremsstrahlung, resembles soft X-rays in its property of penetration. The higher the atomic number or density of the absorbing material, the greater the energy of the Bremsstrahlung produced. Elements of low atomic number produce low-energy Bremsstrahlung, which is readily absorbed; therefore, materials of low atomic number or of low density, such as aluminum, glass, or transparent plastic, are used to shield sources of beta radiation.

Gamma-ray radiation is deeply penetrating. Attenuation of gamma-ray radiation in matter is exponential and usually is expressed in terms of half-value layers. The half-value layer is the thickness of shielding material necessary to decrease the intensity of radiation to half its initial value. A shield of seven half-value thicknesses will reduce the radiation to less than 1 percent of its unshielded intensity of activity. Gamma-ray radiation is commonly shielded with lead.

Intensity of radiation is diminished according to the inverse square of the intervening distance between the source and the point of reference. Radioactive materials of multimillicurie strength can be handled safely in the laboratory by use of proper shielding and/or by arranging for the maximum practicable distance between the source and the operator by means of remote handling devices.

U. S. P. Reference Standards

Reference Standards are called for in many pharmacopeial assays and tests. Originally introduced for the biological assays of U. S. P. X, the use of reference standards has been extended to the point where they are now required for numerous other pharmacopeial assays as well. Some standards formerly required are still being distributed as a service to pharmacy and medicine for use as needed in unofficial assays.

On occasion, as a possible first step in pharmacopeial standardization, a reference standard or substance is provided as a standardized source of endocrine or enzyme activity in advance of the actual pharmacopeial recognition of a product representing that activity. In these cases, the articles supplied are designated as "substances" if they are heterogeneous in nature and if the prospect of their assuming pharmacopeial status is fairly remote; however, heterogeneous substances may be designated as "reference standards" if they are the counterparts of international standards.

The U. S. P. Reference Standards and U. S. P. Reference Substances are released under the authority of the U. S. P. Board of Trustees upon recommendation by the U. S. P. Reference Standards Committee, which supervises the testing and finally passes upon the suitability of each lot. The critical characteristics of the specimens selected for the standard are usually determined independently in three or more laboratories. At the request of the U. S. P. Reference Standards Committee, the Drug Standards Laboratory (see *Preface*) and the Food and Drug Administration laboratory test almost all new Standards and replacements for existing Standards. In addition, laboratories throughout the nation, both academic and industrial, participate in the testing.

A similar program to provide international standards is maintained by the World Health Organization, an agency of the United Nations. The WHO program is concerned mainly with standards for serums, toxins, vaccines, endocrine extracts, and vitamins. As a rule, an International Standard is no longer provided once the substance responsible for its characteristic activity has been isolated, identified, and

made readily available. A limited number of such compounds are distributed under WHO sponsorship as Authentic Chemical Substances for use in assays and tests of drugs. The U. S. P. Reference Standards Committee collaborates closely with the WHO in order not only to minimize unavoidable differences in the actual units of potency but also in some cases to share in the preparation of a reference standard.

No radioactive U. S. P. Reference Standards are provided, because of the special circumstances surrounding the preparation, storage, and distribution of standardized forms of radioactive substances suitable for use in drug analyses, despite the fact that some are called for in pharmacopeial assays and tests. Reliable standards of some radioactive substances, including chromium 51, cobalt 60, gold 198, iodine 131, and phosphorus 32, are available upon order from commercial sources.

Reference Standards are not available for substances subject to the licensing provisions established for narcotics.

The following U. S. P. Reference Standards are available (the Melting Point Standards are shown in *Italics*, where listed individually).

Acetanilid
Acetazolamide
Allopurinol
Amitriptyline Hydrochloride
Amobarbital
Amphotericin B
Ampicillin
Ascorbic Acid
Aspirin
Atropine Sulfate
Benzalkonium Chloride
Benzathine Penicillin G
Gamma Benzene Hexachloride
Benztropine Mesylate
Betazole Hydrochloride
Bishydroxycoumarin
Caffeine
Calcium Disodium Edetate
Calcium Pantothenate
Carbachol
Chlorambucil
Chloramphenicol
Chlordiazepoxide Hydrochloride
Chlorobenzenes
Chloroquine Phosphate
Chlorpheniramine Maleate
Chlorpromazine Hydrochloride
Chlorpropamide
Chlorthalidone
Cholecalciferol[1]
Cholestyramine Resin
Cortirotropin
Cortisone Acetate
Cyanocobalamin
Cyclizine Hydrochloride
Cyclophosphamide
Cycloserine
Demecarium Bromide
Deslanoside
Desoxycorticosterone Acetate
Dexamethasone
Dexamethasone Phosphate
Dextroamphetamine Sulfate
Diaminodiphenylsulfone
Dibucaine Hydrochloride
Dichlorphenamide
Diethylstilbestrol
Diethyltoluamide
Digitalis
Digitoxin
Digoxin
Dihydrostreptomycin Sulfate
Dihydrotachysterol
Dioctyl Sodium Sulfosuccinate
Diphenhydramine Hydrochloride
Diphenylhydantoin
Disodium Edetate
Dyclonine Hydrochloride
Edrophonium Chloride
Epinephrine Bitartrate
Equilin
Ergocalciferol[2]
Ergonovine Maleate
Erythromycin
Erythromycin Ethylcarbonate
Erythromycin Gluceptate[3]
Erythromycin Lactobionate
Estradiol Valerate
Estrone
Ethacrynic Acid
Ethinyl Estradiol
Ethionamide
Ethosuximide
Ethoxzolamide
Ethynodiol Diacetate
Evans Blue
Fluorouracil
Fluoxymesterone
Folic Acid
Furosemide
Gallamine Triethiodide
Gentamicin Sulfate
Globin
Glucagon
Chorionic Gonadotropin
Griseofulvin
Guanethidine Sulfate
Hexachlorophene
Histamine Dihydrochloride
Homatropine Hydrobromide
Hydrochlorothiazide
Hydrocortisone
Hydrocortisone Acetate
Hydrocortisone Sodium Phosphate
Hydrocortisone Sodium Succinate

[1] Formerly called Activated 7-Dehydrocholesterol.

[2] Formerly called Calciferol.

[3] Formerly called Erythromycin Glycoheptonate.

Hydroxychloroquine Sulfate
Hydroxyprogesterone Caproate
Hydroxystilbamidine Isethionate
Idoxuridine
Imipramine Hydrochloride
Indocyanine Green
Insulin
Iodipamide
Iodochlorhydroxyquin
Iothalamic Acid
Isoproterenol Hydrochloride
Kanamycin Sulfate
Levallorphan Tartrate
Levarterenol Bitartrate
Lincomycin Hydrochloride
Liothyronine
Lucanthone Hydrochloride
Mecamylamine Hydrochloride
Meclizine Hydrochloride
Medroxyprogesterone Acetate
Melphalan
Melting Point Standards
Meprobamate
Mercaptopurine
Mestranol
Metaraminol Bitartrate
Methamphetamine Hydrochloride
Methazolamide
Methimazole
Methotrexate Reference Substance
Methyldopa
Methyldopate Hydrochloride
Methylene Blue
Methylergonovine Maleate
Methylphenidate Hydrochloride
Metyrapone
Neomycin Sulfate
Neostigmine Bromide
Neostigmine Methylsulfate
Niacinamide
Nitrofurantoin
Norethindrone
Norethynodrel
Novobiocin
Nystatin
Ouabain
Oxytetracycline
Oxytetracycline Hydrochloride
Phenacetin
Phenacetin
Phenformin Hydrochloride
Phenobarbital
Phenolsulfonphthalein
Phenoxymethyl Penicillin
Phentolamine Mesylate[4]
Phenylephrine Hydrochloride
Physostigmine Salicylate
Phytonadione
Pilocarpine Nitrate
Posterior Pituitary
Negative Control Plastic
Polymyxin B Sulfate
Pralidoxime Chloride
Prednisolone
Prednisolone Acetate
Prednisone
Primidone
Probenecid
Procaine Hydrochloride
Prochlorperazine Maleate
Promethazine Hydrochloride
Proparacaine Hydrochloride
Propoxyphene Hydrochloride
Protamine
Pyrazinamide
Pyridostigmine Bromide
Pyridoxine Hydrochloride
Pyrimethamine
Pyrvinium Pamoate
Quinacrine Hydrochloride
Quinethazone
Quinidine Gluconate
Reserpine
Resorcinol
Riboflavin
Scopolamine Hydrobromide
Secobarbital
Sodium Ampicillin
Sodium Cephalothin
Sodium Cloxacillin
Sodium Colistimethate
Sodium Diatrizoate
Sodium Heparin[4]
Sodium Methicillin
Sodium Nafcillin
Sodium Oxacillin
Sodium Penicillin G
Sodium Sulfobromophthalein
Spironolactone
Streptomycin Sulfate
Sulfadiazine
Sulfamerazine
Sulfamethazine
Sulfanilamide
Sulfanilamide
Sulfapyridine
Sulfisoxazole
Testosterone Cypionate[5]
Testosterone Enanthate
Testosterone Propionate
Tetracaine Hydrochloride
Tetracycline Hydrochloride
Theophylline
Thiabendazole
Thiamine Hydrochloride
Thiopental
Thioridazine Hydrochloride
Thiotepa
Tolazamide
Tolbutamide
Tolnaftate
Triamcinolone
Triamcinolone Acetonide
Triamterene
Trihexyphenidyl Hydrochloride

[4] Formerly called Phentolamine Methanesulfonate.

[4] Formerly called Heparin Sodium.
[5] Formerly called Testosterone Cyclopentylpropionate.

Trimethaphan Camsylate
Tripelennamine Citrate
Tripelennamine Hydrochloride
Tropicamide
Tubocurarine Chloride
Vancomycin Hydrochloride
Vanillin
Vanillin
Vinblastine Sulfate
Vincristine Sulfate
Viomycin Sulfate
Vitamin A
Vitamin D Capsules
Vitamin D Oil
Warfarin
Zinc Bacitracin

Reference Standards and Reference Substances are available on a self-sustaining basis through orders addressed to: U. S. P. Reference Standards, 4630 Montgomery Ave., Bethesda, Md. 20014.

Spectrophotometry, Colorimetry, Turbidimetry, Nephelometry, and Fluorometry

Absorption spectrophotometry is the measurement of the absorption, by substances, of electromagnetic radiation of definite and narrow wavelength range, approximating monochromatic radiation. *Colorimetry* is the commonly accepted term for the measurement of light absorption, usually in the visible spectrum. *Turbidimetry* involves measurement of the degree of attenuation of a light beam incident on particles suspended in a medium, the measurement being made in the directly transmitted beam. *Nephelometry* involves measurement of the light scattered by suspended particles, the measurement usually being made perpendicularly to the incident beam. *Fluorometry* is the measurement of fluorescence, the light or other radiation emitted from a substance while it is being exposed to radiant energy.

The wavelength range available for these measurements extends from the short wavelengths of the ultraviolet through the infrared. For convenience of reference, this spectral range is roughly divided into the ultraviolet (185 mμ to 380 mμ), the visible (380 mμ to 780 mμ), the near-infrared (780 mμ to 3000 mμ), and the infrared (3 μ to 40 μ).

Comparative Utility of Spectral Ranges—For many pharmaceutical substances, measurements can be made in the ultraviolet and visible regions of the spectrum with greater accuracy and sensitivity than in the near-infrared and infrared. When solutions are observed in 1-cm. cells, concentrations of about 10 mcg. of the sample per ml. often will produce absorbances of 0.2 to 0.8. In the infrared and near-infrared, concentrations of 1 to 10 mg. per ml. and up to 100 mg. per ml., respectively, may be needed to produce sufficient absorption: for these spectral ranges, cell lengths of from 0.01 mm. to upwards of 3 mm. are commonly used.

The ultraviolet and visible spectra of a substance generally do not have as high a degree of selectivity as the infrared spectrum. Nevertheless, for many substances they are a useful means of identification and quantitative assay.

The infrared spectrum is usually unique for any given chemical compound with the exception of optical isomers, which have identical spectra. However, polymorphism may occasionally give rise to important differences in the infrared spectrum of a given compound in the solid state. Frequently, small differences in structure result in significant differences in spectra. Because of the large number of absorption bands in an infrared absorption spectrum, it is sometimes possible to measure quantitatively the individual components of a mixture of known qualitative composition without prior separation.

Theory and Terms—The power of a radiant beam decreases in relation to the distance that it travels through an absorbing medium. It also decreases in relation to the concentration of absorbing molecules or ions encountered in that medium. These two factors determine the proportion of the total incident energy that emerges in a relationship known as Beer's law.

The following definitions of spectrophotometric terms and symbols are here designated for pharmacopeial purposes:

Absorbance [Symbol: A]—The logarithm, to the base 10, of the reciprocal of the transmittance (T). (NOTE—Descriptive terms used formerly include optical density; absorbancy; and extinction.)

Absorptivity [Symbol: a]—The quotient of the absorbance (A) divided by the product of the concentration, expressed in *g.* per liter, of the substance and the absorption path length in cm. (NOTE—It is not to be confused with absorbancy index; specific extinction; or extinction coefficient.)

Molar Absorptivity [Symbol: ϵ]—The quotient of the absorbance (A) divided by the product of the concentration, expressed in *moles* per liter, of the substance and the absorption path length in cm. It is also

connected in series by means of glass and inert plastic tubing and suitable stoppers of glass, polymer, or cork (avoiding all use of rubber). Use one tube for the blank and the other for the sample. Arrange a gas-dispersion tube so that the hydrogen issues as bubbles at the bottom of each tube. Pass the hydrogen first through the blank tube and then through the sample tube.

Procedure—Pipet into a suitable vessel 25 ml. of the washed ether solution of the unsaponifiable fraction obtained as directed for *When Tocopherol Is Present* under *Procedure* in the *Vitamin A Assay*, page 914, and evaporate to about 5 ml. *Without applying heat*, remove the remaining ether in a stream of inert gas or by vacuum. Dissolve the residue in sufficient alcohol to give an expected concentration of about 0.15 mg. of alpha tocopherol per ml. Pipet 15 ml. into a 50-ml. centrifuge tube, add approximately 200 mg. of palladium catalyst, stir with a glass rod, and hydrogenate for 10 minutes in the *Hydrogenator*, using hydrogen that has been passed through alcohol in a blank tube. Add about 500 mg. of chromatographic siliceous earth, stir with a glass rod, and immediately centrifuge until the solution is clear.

Test a 1-ml. aliquot of the solution by removing the solvent by evaporation, dissolving the residue in 1 ml. of chloroform, and adding 10 ml. of antimony trichloride T.S.: no detectable blue color appears. [NOTE—If a blue color appears, repeat the hydrogenation for a longer time period, or with a new lot of catalyst.]

Pipet 2 ml. of the supernatant solution into a glass-stoppered, opaque flask, add 1.0 ml. of a 1 in 500 solution of ferric chloride in dehydrated alcohol,* and begin timing the reaction, preferably with a stop watch. Add immediately 1.0 ml. of a 1 in 200 solution of 2,2′-bipyridine in dehydrated alcohol, mix with swirling, add 21.0 ml. of dehydrated alcohol, close the tube, and shake vigorously to ensure complete mixing. When about 90 minutes has elapsed from the beginning of the reaction, transfer part of the mixture to one of a pair of matched 1-cm. spectrophotometer cells. After 10 minutes, accurately timed, following the addition of the ferric chloride-dehydrated alcohol solution, determine the absorbance at 520 mμ, with a suitable spectrophotometer, against dehydrated alcohol as the blank. Perform a blank determination with the same quantities of the same reagents and in the same manner, but using 2 ml. of dehydrated alcohol in place of the 2 ml. of the hydrogenated solution. Subtract the absorbance determined for the blank from that determined for the sample, and designate the difference as A_Z.

Calculate the alpha tocopherol content, in mg., in the sample taken by the formula $30.2 A_Z/(LC_Z)$, in which A_Z is the corrected absorbance, L is the length, in cm., of the absorption cell, and C_Z is the content of the sample in the alcohol solution employed for the measurement of absorbance, expressed as g., capsules, or tablets per 100 ml.

* NOTE—The absorbance of the blank sometimes can be reduced, and the precision of the determination thereby improved, by purification of the dehydrated alcohol that is used throughout the assay. Purification may be accomplished by the addition of a few crystals (about 0.02 percent) of potassium permanganate and of a few pellets of potassium hydroxide to the dehydrated alcohol, and subsequent redistillation.

Vitamin A Assay

The following procedure is provided for the determination of vitamin A as an ingredient of Pharmacopeial preparations. It conforms to that which was adopted in 1956 for international use by the International Union of Pure and Applied Chemistry.

Complete the assay promptly, and exercise care throughout the procedure to keep to a minimum the exposure to actinic light and to atmospheric oxygen and other oxidizing agents, preferably by the use of non-actinic glassware and an atmosphere of an inert gas.

Special Reagents—

ETHER—Use *Ether*, page 219, freshly redistilled, discarding the first and last 10-percent portions.

Procedure—Accurately weigh, count, or measure a portion of the sample expected to contain the equivalent of not less than 0.15 mg. of retinol but containing not more than 1 g. of fat. If in the form of capsules, tablets, or other solid, reflux the portion taken in 10 ml. of water on a steam bath for about 10 minutes, crush the remaining solid with a blunt glass rod, and warm for about 5 minutes longer.

Transfer to a saponification flask,* and add 30 ml. of alcohol if the sample is liquid or 23 ml. of alcohol and 7 ml. of glycerin if the sample is solid, followed by 3 ml. of potassium hydroxide solution (9 in 10). Reflux in an *all-glass* apparatus for 30 minutes. Cool the solution, add 30 ml. of water, and transfer to a conical separator. Add 2 g. of finely powdered sodium sulfate. Extract by shaking for 2 minutes with one 150-ml. portion of ether, and, if an emulsion forms, with three additional 25-ml. portions

of ether. Combine the ether extracts, if necessary, and wash by swirling gently with 50 ml. of water. Repeat the washing more vigorously with three additional 50-ml. portions of water. Transfer the washed ether extract to a 250-ml. volumetric flask, and add ether to volume.

Evaporate a 25.0-ml. portion of the ether extract to about 5 ml. *Without applying heat and with the aid of a stream of inert gas or vacuum,* continue the evaporation to about 3 ml. Dissolve the residue in sufficient isopropyl alcohol to give an expected concentration of the equivalent of 3 to 5 mcg. of vitamin A per ml. or such that it will give an absorbance in the range 0.5 to 0.8 at 325 mμ. Determine the absorbances of the resulting solution at the wavelengths 310 mμ, 325 mμ, and 334 mμ, with a suitable spectrophotometer fitted with matched quartz cells.

WHEN TOCOPHEROL IS PRESENT—Transfer to a saponification flask a suitable sample, accurately measured, or not less than 5 previously crushed Decavitamin Capsules or Decavitamin Tablets. Reflux in an *all-glass* apparatus with 30 ml. of alcohol and 3 ml. of potassium hydroxide solution (9 in 10) for 30 minutes. Add through the condenser 2.0 g. of hydrous citric acid, washing the wall of the condenser with 10 ml. of water. Cool, and transfer the solution to a conical separator with the aid of 20 ml. of water. Add 2 g. of finely powdered sodium sulfate. Extract with one 150-ml. portion of ether, and, if an emulsion forms, with three additional 25-ml. portions of ether. Combine the ether extracts, if necessary, and wash by swirling gently with 50 ml. of water. Repeat the washing more vigorously with three additional 50-ml. portions of water. Transfer the washed ether extract to a 250-ml. volumetric flask, and add ether to volume. Transfer a 100.0-ml. aliquot of the resulting ether solution to a conical separator, and wash once with 50 ml. of potassium hydroxide solution (1 in 33), using alcohol, if necessary, to break any emulsion that forms. Wash by swirling gently with 50 ml. of water. Repeat the washing more vigorously with three additional 50-ml. portions of water. Transfer the washed ether extract to a 100-ml. volumetric flask, and add ether to volume.

Evaporate a 50.0-ml. aliquot of the ether solution of the unsaponifiable extract to about 5 ml. *Without applying heat and with the aid of a stream of inert gas or vacuum,* remove the residual ether. Dissolve the residue in 50.0 ml. of isopropyl alcohol.

Hydrogenated portion—Pipet 15 ml. of the isopropyl alcohol solution into a 50-ml. centrifuge tube, add approximately 200 mg. of palladium catalyst, stir with a glass rod, and hydrogenate for 10 minutes in a *Hydrogenator* such as is described in the *Alpha Tocopherol Assay*, page 913, using isopropyl alcohol in the blank tube. Add about 300 mg. of chromatographic siliceous earth, stir with a glass rod, and immediately centrifuge until the solution is clear.

Test a 1-ml. aliquot of the solution by removing the solvent by evaporation, dissolving the residue in 1 ml. of chloroform, and adding 10 ml. of antimony trichloride T.S.: no detectable blue color appears. [NOTE—If a blue color appears, repeat the hydrogenation for a longer time period, or with a new lot of catalyst.]

Into two separate flasks pipet equal volumes of the *Hydrogenated portion* and the untreated isopropyl alcohol solution, respectively, and add sufficient isopropyl alcohol to give an expected concentration of vitamin A equivalent to 3 mcg. to 5 mcg. per ml. Determine the absorbances of the untreated solution against the solution from the *Hydrogenated portion* as a blank, at the wavelengths 310 mμ, 325 mμ, and 334 mμ, with a suitable spectrophotometer fitted with matched quartz cells.

Calculation—Calculate the vitamin A content as follows:

$$\text{Content (in mg.)} = 0.549A_{325}/LC,$$

in which A_{325} is the observed absorbance at 325 mμ, L is the length, in cm., of the absorption cell, and C is the amount of sample expressed as g., capsule, or tablet in each 100 ml. of the final isopropyl alcohol solution, provided that A_{325} has a value not less than $[A_{325}]/1.030$ and not more than $[A_{325}]/0.970$, where $[A_{325}]$ is the *corrected* absorbance at 325 mμ and is given by the equation $[A_{325}] = 6.815A_{325} - 2.555A_{310} - 4.260A_{334}$, in which A designates the absorbance at the wavelength indicated by the subscript.

Where $[A_{325}]$ has a value less than $A_{325}/1.030$, apply the following equation:

$$\text{Content (in mg.)} = 0.549[A_{325}]/LC,$$

in which the values are as defined herein.

Confidence Interval—The range of the limits of error, indicating the extent of discrepancy to be expected in the results of different laboratories at $P = 0.05$, is approximately ±8 percent.

Vitamin D Assay

The following procedure is provided for the determination of vitamin D as an ingredient of Pharmacopeial preparations.

Complete the assay promptly, and exercise care throughout the procedure to keep to a minimum the exposure to air and to

actinic light, preferably by the use of a blanket of inert gas and low-actinic glassware.

Special Reagents and Solutions—

CHROMATOGRAPHIC FULLER'S EARTH—Use chromatographic fuller's earth having a water content corresponding to not less than 8.5 percent and not more than 9.0 percent of loss on drying.

SOLVENT HEXANE—Use solvent hexane (see under *Reagents*), redistilling if necessary so that it meets the following additional specification:

Spectral purity—Measure in a 1-cm. cell at 300 mμ, with a suitable spectrophotometer, against air as the blank: the absorbance is not more than 0.070.

ETHYLENE DICHLORIDE—Purify by passage through a column of granular (20 to 200 mesh) silica gel.

POTASSIUM HYDROXIDE SOLUTION—Dissolve 500 g. of potassium hydroxide in water to make 1000 ml.

BUTYLATED HYDROXYTOLUENE SOLUTION—Dissolve 10 mg. of butylated hydroxytoluene in 100 ml. of alcohol. Prepare this solution fresh daily.

COLOR REAGENT—Prepare two stock solutions as follows.

Solution A—Empty, without weighing, the entire contents of a previously unopened 113-g. bottle of dry, crystalline antimony trichloride into a flask containing about 400 ml. of *Ethylene Dichloride*. Add about 2 g. of anhydrous alumina, mix, and filter through filter paper into a clear-glass, glass-stoppered container calibrated at 500 ml. Add *Ethylene Dichloride* to make 500 ml., and mix: the absorbance of the solution, measured in a 20-mm. cell at 500 mμ, with a suitable spectrophotometer, against *Ethylene Dichloride*, does not exceed 0.070.

Solution B—Mix, under a hood, 100 ml. of acetyl chloride and 400 ml. of *Ethylene Dichloride*.

Mix 45 ml. of *Solution A* and 5 ml. of *Solution B* to obtain the *Color Reagent*. Store in a tight container, and use within 7 days, but discard any reagent in which a color develops.

Chromatographic Tubes—

FIRST COLUMN—Arrange for descending column chromatography a tube of 2.5-cm. (inside) diameter, about 25 cm. long, and constricted to 8-mm. diameter for a distance of 5 cm. at the lower end, by inserting at the point of constriction a coarse-porosity, sintered-glass disk or a small plug of glass wool. The constricted portion may be fitted with an inert, plastic stopcock.

SECOND COLUMN—Select a tube that is made up of three sections: (1) a flared top section, 18 mm. in (inside) diameter and approximately 14 cm. long, (2) a middle section, 6 mm. in (inside) diameter and approximately 25 cm. long, and (3) a tapered, constricted lower exit tube approximately 5 cm. long. Insert a small plug of glass wool in the upper 1-cm. portion of the constricted section.

Chromatographic Columns—

FIRST COLUMN—To about 125 ml. of isooctane contained in a screw-capped, wide-mouth bottle add 25 g. of chromatographic siliceous earth, and shake until a slurry is formed. Add, dropwise and with vigorous mixing, 10 ml. of polyethylene glycol 600. Replace the bottle cover, and shake vigorously for 2 minutes. Pour about half of the resulting slurry into the chromatographic tube, and allow it to settle by gravity. Then apply gentle suction, and add the remainder of the slurry in small portions, packing each portion with a 20-mm. disk plunger. When a solid surface has formed, remove the vacuum, and add about 2 ml. of isooctane.

SECOND COLUMN—Pack the midsection of the tube with 3 g. of moderately coarse *Chromatographic Fuller's Earth* with the aid of gentle suction (about −125 mm. of mercury).

Standard Preparation—Dissolve about 25 mg. of U. S. P. Ergocalciferol Reference Standard, accurately weighed, in sufficient isooctane to give a known concentration of about 250 mcg. per ml. Store in a refrigerator.

On the day of assay, pipet 1 ml. of the standard solution into a 50-ml. volumetric flask, remove the solvent with a stream of nitrogen, and dissolve the residue in, and make to volume with, *Ethylene Dichloride*.

Sample Preparation—Accurately weigh or measure a portion of the sample to be assayed, equivalent to not less than 125 mcg. but preferably about 250 mcg. of ergocalciferol (10,000 U. S. P. Units). If little or no vitamin A is present in the sample, add about 1.5 mg. (the equivalent of 3000 U. S. P. Units) of vitamin A acetate to provide the needed pilot bands in the subsequent chromatography.

For capsules or tablets, reflux not less than 10 of them in 10 ml. of water on a steam bath for about 10 minutes, crush the remaining solid with a blunt glass rod, and warm for 5 minutes longer.

Add a volume of *Potassium Hydroxide Solution* representing 2.5 ml. for each g. of the total weight of the sample, but not less than a total of 3.0 ml. Add 10 ml. of *Butylated Hydroxytoluene Solution* and 20 ml. of alcohol. Reflux vigorously on a steam bath for 30 minutes. Cool, and transfer the saponified mixture to a conical separator, rinsing the saponification flask with three 10-ml. portions of water and three 50-ml. portions of ether, adding each rinse to the separator. Add about 4 g. of sodium sulfate decahydrate to the separator,

and extract by shaking for 2 minutes. If an emulsion forms, extract with three 25-ml. portions of ether. Combine the ether extracts, if necessary, and wash by swirling gently with 50 ml. of water. Repeat the washing more vigorously with additional 50-ml. portions of water until the last portion shows no pink color on the addition of phenolphthalein T.S. Transfer the washed ether extract to a 250-ml. volumetric flask, add ether to volume, and mix. Transfer the entire sample or an accurately measured aliquot containing about 250 mcg. to a tall-form, 400-ml. beaker containing about 5 g. of anhydrous sodium sulfate. Stir for 2 minutes, then decant the solution into a second 400-ml. beaker. Rinse the sodium sulfate with three 25-ml. portions of ether, adding each rinse to the main portion. Reduce the total volume to about 30 ml. by evaporation on a steam bath, and transfer the concentrate to a small, round-bottom evaporation flask. Rinse the beaker with three 10-ml. portions of ether, adding the rinsings to the flask. With the aid of vacuum in a water bath at a temperature not exceeding 40°, or with a stream of nitrogen at room temperature, remove the remaining solvent completely. Dissolve the residue in a small amount of *Solvent Hexane*, transfer to a 10-ml. volumetric flask, and dilute with *Solvent Hexane* to volume to obtain the *Sample Preparation*.

Procedure—

FIRST COLUMN CHROMATOGRAPHY—Just as the 2 ml. of isooctane disappears into the surface of the prepared *First Column*, pipet 2 ml. of the *Sample Preparation* onto the column. As the meniscus of the *Sample Preparation* reaches the column surface, add the first of three 2-ml. portions of *Solvent Hexane*, adding each succeeding portion as the preceding portion disappears into the column. Continue adding *Solvent Hexane* in portions of 5 to 10 ml. until 100 ml. has been added. If necessary, adjust the flow rate to between 3 and 6 ml. per minute, by application of gentle pressure at the top of the chromatographic tube.

Discard the first 20 ml. of effluent, and collect the remainder. Examine the column under ultraviolet light at intervals during the chromatography, and stop the flow when the front of the fluorescent band representing vitamin A is about 5 mm. from the bottom of the column. (The ultraviolet lamp should provide *weak* radiation in the 300-mμ region. It is frequently necessary to use a narrow aperture or screen with commercial lamps to reduce the amount of radiation to the minimum required to visualize the vitamin A on the column.)

Transfer the eluate to a suitable evaporation flask, and remove the solvent hexane completely under vacuum at a temperature not above 40° or with a stream of nitrogen at room temperature. Dissolve the residue in about 10 ml. of *Solvent Hexane*.

SECOND COLUMN CHROMATOGRAPHY—Add the solvent hexane solution obtained as directed under *First Column Chromatography* onto the *Second Column*. Rinse the evaporation flask with a total of 10 ml. of *Solvent Hexane* in small portions, adding each portion to the *Second Column* and allowing it to flow through the column, and discard the effluent. When about 1 ml. of the solvent hexane remains above the surface of the column, add 75 ml. of benzene, and elute with the aid of gentle suction (about −125 mm. of mercury), collecting the eluate. Evaporate the benzene under vacuum at a temperature not above 40°, or with a stream of nitrogen at room temperature.

ASSAY PREPARATION—Dissolve the residue obtained as directed under *Second Column Chromatography* in a small amount of *Ethylene Dichloride*, transfer to a 10-ml. volumetric flask, and make to volume with *Ethylene Dichloride* to obtain the *Assay Preparation*.

COLOR DEVELOPMENT—Into each of three suitable, matched colorimeter tubes of about 20-mm. (inside) diameter, and designated *1*, *2*, and *3*, respectively, pipet 1 ml. of the *Assay Preparation*. Into tube *1* pipet 1 ml. of the *Standard Preparation*, into tube *2*, 1 ml. of *Ethylene Dichloride*, and into tube *3*, 1 ml. of a mixture of equal volumes of acetic anhydride and *Ethylene Dichloride*. To each tube add quickly, and preferably from an automatic pipet, 5.0 ml. of *Color Reagent*, and mix. After 15 seconds, accurately timed, following the addition of the color reagent, determine the absorbances of the three solutions at 500 mμ, with a suitable spectrophotometer, using *Ethylene Dichloride* as the blank. Similarly, 45 seconds after making the first reading on each solution, determine the absorbances of the solutions in tubes *2* and *3* at 550 mμ, in a similar manner. Designate the absorbances as A^1_{500}, A^2_{500}, A^3_{500}, A^2_{550}, and A^3_{550}, respectively, in which the superscript indicates the number of the tube and the subscript the wavelength.

Calculation—Calculate the quantity, in mcg., of vitamin D in the portion of the sample taken by the formula $(C_S/C)(A_U/A_S)$, in which C_S is the concentration of vitamin D in mcg. per ml. of the *Standard Preparation*, C is the concentration of the sample (as g., capsules, tablets, etc.) in each ml. of the final solution, A_U has the value of $(A^2_{500} - A^3_{500}) - 0.67(A^2_{550} - A^3_{550})$ determined from the absorbances observed on the solution from the *Assay Preparation*, and A_S has the value of $A^1_{500} - A^3_{500}$ determined on the solution from the *Standard Preparation*.

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tions and conversion charts obtainable from the American Society for Testing and Materials.

Procedure for Cellulose Derivatives—Measurement of the viscosity of solutions of the high-viscosity types of cellulose derivatives is a special case, since they are too viscous for the commonly available viscosimeters. The Ubbelohde viscosimeter may be adapted as illustrated in the accompanying illustration (or ASTM, D-1347), to the measurement of the ranges of viscosity encountered in methylcellulose solutions.

Calibration of the Ostwald Type Viscosimeter—Determine the viscosimeter constant, k, for each viscosimeter by the use of an oil of known viscosity.† Place an excess of the oil (adjusted to 20 ± 0.1°) in the filling tube and transfer it to the orifice tube by gentle suction, taking care to prevent bubble formation in the liquid by keeping the air vent tube closed. Adjust the meniscus of the column of liquid in the orifice tube to the level of the top graduation line. Open both the vent and orifice tubes in order to permit the liquid to flow into the reservoir against atmospheric pressure. (Failure to open the vent tube before releasing the orifice tube will yield false values.) Record the time in seconds for the liquid to flow from the upper mark to the lower mark in the orifice tube.

Calculate the viscosimeter constant, k, from the equation $k = v/dt$, in which v is the known viscosity of the liquid in centipoises, d is the specific gravity of the liquid tested at 20°/20°, and t is the time in seconds for the liquid to pass from the upper mark to the lower mark.

If a viscosimeter is repaired, it must be recalibrated, since even minor repairs frequently cause significant changes in the value of its constant, k.

† Oils of known viscosities formerly supplied by the National Bureau of Standards, may be obtained from the Cannon Instrument Co., Post Office Box 16, State College, PA 16801. For methylcellulose, choose an oil the viscosity of which is as close as possible to that of the type of methylcellulose to be determined.

VITAMIN A ASSAY

Complete the assay promptly and exercise care throughout the procedure to avoid undue exposure to oxidizing agents, to actinic light, and to other conditions that destroy vitamin A. The use of nonactinic glassware is advantageous in avoiding destruction by light.

Isopropyl alcohol—Use *Isopropyl Alcohol*, distil, if necessary, to meet the following requirements for spectral purity: when measured in a 1-cm. cell against distilled water it shows an absorbance not greater than 0.05 at 300 mμ and not greater than 0.01 between 320 mμ and 350 mμ.

Ether—Use *Ether*, freshly distilled, discarding the first and last 10 percent portions, or *Ether*, anesthetic grade, from a freshly opened container.

Saponification—Transfer to a saponification flask an amount of the sample, accurately measured and expected to contain not less than the equivalent of 150 mcg. of vitamin A, but not more than 1 g. of fat: Reflux in an *all-glass* apparatus with 30 ml. of alcohol and 3 ml. of potassium hydroxide solution (1 in 2) for 30 minutes. Cool the solution, add 30 ml. of water, and transfer the resulting solution to a conical separator. Add 2 g. of finely powdered sodium sulfate. Extract, by shaking for 2 minutes, with one 150-ml. portion of ether, or, if an emulsion occurs, with three additional 25-ml. portions of ether. Combine the ether extracts, if necessary, and wash by swirling gently with 50 ml. of water. Repeat the washing more vigorously until the last washing gives no color with phenolphthalein T.S. Transfer the washed ether extract to a 250-ml. volumetric flask, and dilute to volume with ether.

Procedure—Evaporate a 25.0-ml. aliquot of the ether solution of the unsaponifiable extract to about 5 ml. Without the application of heat, reduce the volume to about 3 ml. in a stream of inert gas or under reduced pressure. Dissolve the residue in sufficient isopropyl alcohol to give an expected concentration of the equivalent of 3 to 5 mcg. of vitamin A per ml. or such that it will give an absorbance in the range 0.4 to 0.8 at 325 mμ. Determine the absorbances of the resulting solution in 1-cm. cells, at 310 mμ, 325 mμ, and 334 mμ with a suitable spectrophotometer, using isopropyl alcohol as the blank.

Calculation—Calculate the vitamin A content as follows: Vitamin A content (in mg.) = $0.549 \times (A_{325}/LC)$, in which A_{325} is the observed absorbance at 325 mμ, L is the length, in cm., of the absorption cell, and C is the amount of sample expressed as g., capsule or tablet, in each 100 ml. of the final isopropyl alcohol solution, provided that A_{325} has a value not less than $A_{325}(\text{cor.})/1.030$ and not more than $A_{325}(\text{cor.})/0.970$, where $A_{325}(\text{cor.}) = 6.815A_{325} - 2.555A_{310} - 4.260A_{334}$, in which A designates the absorbance at the wavelengths indicated by the subscripts. Where $A_{325}(\text{cor.})$ has a value less than $A_{325}/1.030$ apply the following formula: Vitamin A content, in mg., $= 0.549[A_{325(\text{cor.})}/LC]$. Each mg. of vitamin A (alcohol)

represents 3333 USP Units of vitamin A.

Confidence Interval—The range of the limits of error, indicating the extent of discrepancy to be expected in the results of different laboratories at $P = 0.05$, is approximately ±8 percent.

VITAMIN B_{12} ACTIVITY ASSAY

Assay Preparation—Place a suitable quantity of the material to be assayed, accurately measured or weighed, in an appropriate vessel containing, for each g. or ml. of sample taken, 25 ml. of an aqueous extracting solution prepared just prior to use to contain, in each 100 ml., 1.29 g. of disodium phosphate, 1.1 g. of anhydrous citric acid, and 1.0 g. of sodium metabisulfite. Autoclave the mixture at 121° for 10 minutes. Allow any undissolved particles of the sample extract to settle, and filter or centrifuge if necessary. Dilute an aliquot of the clear solution with water so that the final test solution contains vitamin B_{12} activity approximately equivalent to that of the *Standard Cyanocobalamin Solution* which is added to the assay tubes.

Standard Cyanobalamin Stock Solution—To a suitable quantity of USP Cyanocobalamin Reference Standard, accurately weighed, add sufficient 25 percent alcohol to make a solution containing, in each ml., 1.0 mcg. of cyanocobalamin. Store in a refrigerator.

Standard Cyanocobalamin Solution—Dilute a suitable volume of *Standard Cyanocobalamin Stock Solution* with water to a measured volume such that after the incubation period as described under *Procedure*, the difference in transmittance between the inoculated blank and the 5.0-ml. level of the *Standard Cyanocobalamin Solution* is not less than that which corresponds to a difference of 1.25 mg. in dried cell weight. This concentration usually falls between 0.01 and 0.04 millimicrogram per ml. of *Standard Cyanocobalamin Solution*. Prepare a fresh standard solution for each assay.

Basal Medium Stock Solution—Add the ingredients in the order listed, carefully dissolving the cystine and tryptophane in the hydrochloric acid before adding the next eight solutions in the resulting solution. Add 100 ml. of water, mix, and dissolve the dextrose, sodium acetate, and ascorbic acid. Filter, if necessary, add the polysorbate 80 solution, adjust the reaction to pH 6.0 with 1 *N* sodium hydroxide, and add purified water to make 250 ml.

L-Cystine	0.1	g.
L-Tryptophane	0.05	g.
1 *N* Hydrochloric Acid	10	ml.
Adenine-Guanine-Uracil Solution	5	ml.
Xanthine Solution	5	ml.
Vitamin Solution I	10	ml.
Vitamin Solution II	10	ml.
Salt Solution A	5	ml.
Salt Solution B	5	ml.
Asparagine Solution	5	ml.
Acid-hydrolyzed Casein Solution	25	ml.
Dextrose, Anhydrous	10	g.
Sodium Acetate, Anhydrous	5	g.
Ascorbic Acid	1	g.
Polysorbate 80 Solution	5	ml.

Acid-hydrolyzed Casein Solution—Mix 100 g. of vitamin-free casein with 500 ml. of dilute hydrochloric acid (1 in 2), and reflux the mixture for 8 to 12 hours. Remove the hydrochloric acid from the mixture by distillation under reduced pressure until a thick paste remains. Redissolve the resulting paste in water, adjust the solution to a pH of 3.5 ± 0.1 with sodium hydroxide solution, and add water to make 1000 ml. Add 20 g. of activated charcoal, stir for 1 hour, and filter. Repeat the treatment with activated charcoal. Store under toluene in a refrigerator at a temperature not below 10°. Filter the solution if a precipitate forms under storage.

Asparagine Solution—Dissolve 2.0 g. of *L*-asparagine in water to make 200 ml. Store under toluene in a refrigerator.

Adenine-Guanine-Uracil Solution—Dissolve 200 mg. each of adenine sulfate, guanine hydrochloride, and uracil, with the aid of heat, in 10 ml. of dilute hydrochloric acid (1 in 3), cool, and add water to make 200 ml. Store under toluene in a refrigerator.

Xanthine Solution—Suspend 0.2 g. of xanthine in 30 to 40 ml. of water, heat to about 70°, add 6.0 ml. of ammonia T.S., and stir until the solid is dissolved. Cool, and add water to make 200 ml. Store under toluene in a refrigerator.

Salt Solution A—Dissolve 10 g. of monobasic potassium phosphate and 10 g. of dibasic potassium phosphate in water to make 200 ml. Add 2 drops of hydrochloric acid, and store under toluene.

Salt Solution B—Dissolve 4.0 g. of magnesium sulfate, 0.2 g. of sodium chloride, 0.2 g. of ferrous sulfate, and 0.2 g. of manganese sulfate in water to make 200 ml. Add 2 drops of hydrochloric acid, and store under toluene.

Polysorbate 80 Solution—Dissolve 20 g. of polysorbate 80 in sufficient alcohol to make 200 ml. Store in a refrigerator.

Vitamin Solution I—Dissolve 10 mg. of riboflavin, 10 mg. of thiamine hydrochloride, 0.1 mg. of biotin, and 20 mg. of nicotinic acid in sufficient 0.02 *N* acetic acid to

VITAMIN D ASSAY

Biological Method

The biological assay of vitamin D comprises the recording and interpretation of observations on groups of rats maintained on specified dietary regimens throughout specified periods of their lives whereby the biological response to the preparation under assay is compared with the response to USP Vitamin D Reference Standard.

Preliminary Period—Throughout the preliminary period in the life of a rat, which is not longer than 30 days and extends from birth to the first day of the depletion period, maintain litters of rats under the immediate supervision of, or according to the directions of, the individual responsible for the assay. During the preliminary period, use a dietary regimen which provides for normal development but is limited in its content of vitamin D, so that when placed upon the *Rachitogenic Diet* in the depletion period the rats develop rickets. At the end of the preliminary period, reject any rat which weighs less than 44 g. or more than 60 g., or which shows evidence of injury, disease, or anatomical abnormality.

Depletion Period—Through the depletion period, which extends from the end of the preliminary period to the first day of the assay period, provide each rat *ad libitum* with the *Rachitogenic Diet* and water and allow access to no other food or dietary supplement.

Rachitogenic Diet—The rachitogenic diet consists of a uniform mixture of the following ingredients in the proportions shown:

	Parts by Weight
Whole Yellow Corn, ground	76
Ground Wheat Gluten	20
Calcium Carbonate	3
Sodium Chloride	1

When a chemical analysis of the entire ration shows a Ca:P ratio of less than 4:1 or more than 5:1, the proportion of calcium carbonate may be varied to bring the adjusted ratio to a uniform level within this range.

Assigning Rats to Groups for the Assay Period—Consider a litter suitable for the assay period when individual rats in the litter show evidence of rickets such as enlarged joints and a distinctive wobbly, rachitic gait, provided that the depletion period is not less than 19 or more than 25 days. The presence of rickets may be established also from the width of the rachitic metaphysis upon X-ray examination or by applying the line test (described below) to a leg bone of one member of each litter.

Record the weight of each rat and assign it to a group, in which each rat will be fed a specified dose of the reference standard or of an assay sample that is under examination for its vitamin D potency. For each assay sample provide one or more assay groups and at least two standard groups. The two standard groups may be used for the concurrent assay of more than one assay sample. Within an interval not exceeding 30 days, complete the assignment of rats to groups according to a design which divides litters among the groups, to achieve a complete balance.

For complete balance, whereby each litter is represented equally in every group, use seven or more litters containing at least as many depleted rats as there are groups. From a given litter, assign one rat, selected at random, to each group on the same day. If a litter contains twice as many rats as there are groups, assign a second series of rats similarly. The last one or two litters to be assigned may be allotted to groups so that at the start of the assay period the average body weight of any completed groups will not differ by more than 8 g. from that of any other group.

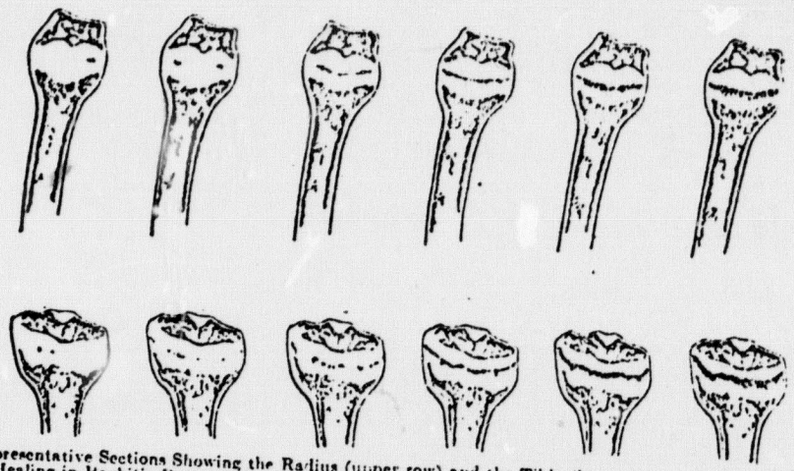
Assay Doses—Select two dosage levels of the USP Vitamin D Reference Standard, spaced so that the ratio of the larger to the smaller dose is not less than 1.5 or more than 2.5. Select one or two dosage levels based upon a single assumed potency for each sample. The dosage levels of the sample are equivalent to those of the standard or to a mid-level equal to the square root of the product of the two dosage levels of the standard.

Select dosage levels such that, when fed to rachitic rats, they are expected to produce degrees of calcification within the range specified under the test of data acceptability. Before feeding, the reference standard and or sample may be diluted with cottonseed oil, provided that not more than 0.2 ml. is fed on any one day. Store the oil solutions in well-closed bottles, protected from light, at a temperature not exceeding 10°, and use within 5 weeks.

Assign one group of rats to each dosage level of the standard and of the one or more samples.

Assay Period—During the assay period, which extends from the end of the depletion period for a fixed interval of 7 to 10 days, cage each rat individually and provide it *ad libitum* with the *Rachitogenic Diet* and water. Supply a rachitogenic diet prepared from the same lots of ingredients to all rats. On the first and on the third (or fourth) day of the assay period, feed each rat one-half of its total assigned dose.

Throughout the assay period, maintain as uniform environmental conditions as possible for all rats and exclude exposure to



Representative Sections Showing the Radius (upper row) and the Tibia (lower row) in Graded Degrees of Healing in Rachitic Rats within the Useful Range of the Dosage-Response Relationship of the Vitamin D Assay

antirachitic radiations. At the end of a fixed period of 7 to 10 days, weigh and kill each rat. From those rats which do not weigh less at the end than at the start of the assay period and which have consumed each assigned dose within 24 hours of the time it was fed, dissect out one or more leg bones for examination by the *Line Test*.

Line Test—Remove the proximal end of a tibia or the distal end of a radius and clean it of adhering tissue, in any one assay using the same bone from all animals. With a clean, sharp blade cut a median, longitudinal section through the juncture of the epiphysis and diaphysis at the same place on each bone. Rinse both sections in purified water, immerse immediately in silver nitrate solution (1 in 50) for 1 minute, and rinse again in purified water. Expose the cut surface of bone, in water, to daylight or another source of actinic light until the calcified areas develop a clearly defined stain without marked discoloration of the uncalcified areas. The staining procedure may be modified to differentiate more clearly between calcified and uncalcified areas.

Score the degree of calcification of the rachitic metaphysis in each rat, according to a scale which allows the average response to be plotted as a straight line against the logarithm of the dose. The figure presented illustrates the range of the degree of calcification best suited for assay purposes.

Acceptability—Observations are acceptable for use in calculation of the potency only from those groups in which two-thirds or more but not less than 7 rats show calcification at least as great as the lowest level and not greater than the highest level illustrated in the figure. If the average score of the standard group on the high dosage level is not greater than the average score of the standard group on the low dosage level, discard the results and repeat the assay. If an assay sample is represented solely by assay groups which are not acceptable for measuring vitamin D potency and in each of which the average score is less than the average score of the standard group on the low dosage level or more than the average score of the standard group on the high dosage level, its assayed content of vitamin D is respectively less than that represented by the low dose or more than that represented by the high dose of the Reference Standard.

Calculation—Tabulate the scores (y), listing each litter in a separate row with treatment groups in columns. Omit any groups which do not meet the test for *Acceptability*. Equalize the number of observations in the acceptable groups by disregarding the results on all litters not equally represented in the groups or by other suitable means (see *Design and Analysis of Biological Assays*, USP XVIII). Total the f scores for each of the treatment groups, where f is the number of litters, and designate each total as T with subscripts 1 and 2 for the low and high dosage levels, respectively. Compute the slope b from the sums of T_1, *i.e.*, ΣT_1, and of T_2, *i.e.*, ΣT_2, for the standard and sample, provided the latter is represented at both dosage levels as $b = (\Sigma T_2 - \Sigma T_1)/ifh'$, where i is the logarithm of the ratio of the high dose to the low dose and is the same for each preparation, and h' is the number of preparations represented by two dosage levels and included in the calculation of the value of b.

Compute the logarithm of the relative potency of each sample under assay as log (relative potency) $= M' = (\bar{y}_T - \bar{y}_S)/b = ih'T_s/2\Sigma T_s$, where each mean score, $\bar{y}_T$ for the assay sample and $\bar{y}_S$ for the Reference

Standard, is the average of the individual scores for an intermediate dosage level or of the two means for the high and the low dosage levels and where $T_s = \Sigma T_2 - \Sigma T_1$ and T_s is defined in USP XVIII. Convert each observed M' to its antilogarithm to obtain the relative potency of the sample. Multiply the relative potency by the assumed potency of the assay oil in Units per g., accepted at the start of the assay, to obtain its assayed content of vitamin D in USP Units per g.

Chemical Method

The following procedure is provided for the determination of vitamin D as an ingredient of official preparations containing other active constituents.

Special Reagents and Solutions—

Chromatographic Fuller's Earth—Use chromatographic fuller's earth having a water content corresponding to not less than 8.5 percent and not more than 9.0 percent of loss on drying.

Solvent Hexane—Use reagent solvent hexane (see USP XVIII), distilling if necessary so that it meets the following additional specification:

Spectral purity—Measure in a 1-cm. cell at 300 mμ, with a suitable spectrophotometer, against air as the blank: the absorbance is not more than 0.070.

Ethylene Dichloride—Purify by passage through a column of granular (20 to 200 mesh) silica gel.

Potassium Hydroxide Solution—Dissolve 780 g. of potassium hydroxide in water to make 1000 ml.

Cottonseed Oil—Use cottonseed oil USP that meets the following additional requirement: Saponify 10 g. of the oil as directed in this chapter under *Sample Preparation*, beginning with "then add a volume of *Potassium Hydroxide Solution*," and dissolve the unsaponifiable residue in 10 ml. of *Solvent Hexane*.

In a separate container place 0.4 ml. of ferric chloride solution (1 in 1000) and 12 ml. of a 1 in 6000 solution of 2,2'-bipyridine in dehydrated alcohol, mix, and 5 minutes later read the absorbance in a 1-cm. cell at 520 mμ, with a suitable spectrophotometer, using dehydrated alcohol as the blank. Then add 0.2 ml. of the solvent hexane solution of the unsaponifiable residue, and after 5 minutes read the absorbance. The difference between the first and the second absorbances is not less than 0.125.

Color Reagent—Prepare two stock solutions as follows.

Solution A—Empty, without weighing, the entire contents of a previously unopened 113-g. bottle of dry, crystalline antimony trichloride into a flask containing about 400 ml. of *Ethylene Dichloride*. Add about 2 g. of anhydrous alumina, mix, and filter through filter paper into a clear-glass, glass-stoppered, container calibrated at 500 ml. Add *Ethylene Dichloride* to make 500 ml., and mix: the absorbance of the solution, measured in a 2-cm. cell at 500 mμ, with a suitable spectrophotometer, against *Ethylene Dichloride*, does not exceed 0.070.

Solution B—Mix, under a hood, 100 ml. of acetyl chloride and 400 ml. of *Ethylene Dichloride*.

Mix 45 ml. of *Solution A* and 5 ml. of *Solution B* to obtain the *Color Reagent*. Store in a tight container, and use within 7 days, but discard any reagent in which a color develops.

Chromatographic Tubes—

First Column—Arrange for descending column chromatography (see page 786) a tube of 2.5 cm. (inside) diameter, about 25 cm. long, and constricted to 8 mm. diameter for a distance of 5 cm. at the lower end, by inserting at the point of constriction a coarse-porosity, sintered-glass disk or a small plug of glass wool. The constricted portion may be fitted with an inert, plastic stopcock.

Second Column—Select a tube that is made up of three sections: (1) a flared top section, 18 mm. in (inside) diameter and approximately 14 cm. long, (2) a middle section, 6 mm. in (inside) diameter and approximately 25 cm. long, and (3) a tapered, constricted lower exit tube approximately 5 cm. long. Insert a small plug of glass wool in the upper 1-cm. portion of the constricted section.

Chromatographic Columns—

First Column—To about 125 ml. of isooctane contained in a screw-cap, wide-mouth bottle add 25 g. of chromatographic siliceous earth, and shake until a slurry is formed. Add, dropwise and with vigorous mixing, 10 ml. of polyethylene glycol 600. Replace the bottle cover, and shake vigorously for 2 minutes. Pour about half of the resulting slurry into the chromatographic tube, and allow it to settle by gravity. Then apply gentle suction, and add the remainder of the slurry in small portions, packing each portion with a 20-mm. disk plunger. When a solid surface has formed, remove the vacuum, and add about 2 ml. of isooctane.

Second Column—Pack the midsection of the tube with 3 g. of moderately coarse *Chromatographic Fuller's Earth* with the aid of gentle suction (about −125 mm. of mercury).

Standard Preparation—Dissolve about 25 mg. of USP Ergocalciferol Reference Standard, accurately weighed, in sufficient isooctane to make 100.0 ml. Store in a refrigerator.

On the day of assay, pipet 1.0 ml. of the standard solution into a 50-ml. volumetric flask, remove the solvent with a stream of nitrogen, and dissolve the residue in, and dilute to volume with, *Ethylene Dichloride*.

Sample Preparation—Unless otherwise

directed, accurately weigh or measure a portion of the sample to be assayed, equivalent to not less than 125 mcg. but preferably about 250 mcg. of ergocalciferol (10,000 USP Units). If little or no vitamin A is present in the sample, add about 1.5 mg. (the equivalent of 5000 USP Units) of vitamin A to provide the needed pilot bands in the subsequent chromatography.

For capsules or tablets, reflux not less than 10 of them in 10 ml. of water on a steam bath for about 10 minutes, crush the remaining solid with a blunt glass rod, and warm for 5 minutes longer.

Add 2 ml. of *Cottonseed Oil*, then add a volume of *Potassium Hydroxide Solution* representing 2.5 ml. for each g. of the total weight of the sample plus cottonseed oil, but not less than 15 ml. Add 50 ml. of alcohol. Reflux vigorously on a steam bath for 20 minutes, or for 30 minutes for samples weighing more than 5 g. If oil globules are evident, indicating incomplete saponification, add 5 ml. of *Potassium Hydroxide Solution* (but not exceeding a total of 100 ml.), and heat again. Cool, and transfer the saponified mixture to a 500-ml. separator, rinsing the saponification flask with a total of 50 ml. of water and adding each rinse to the separator. Add about 4.5 g. of sodium sulfate decahydrate and 150 ml. of *Solvent Hexane*. Shake vigorously for 2 minutes. When the aqueous layer has separated, transfer it to a second separator. Extract with two 50-ml. portions of *Solvent Hexane*, combine the extracts, and discard the aqueous solution.

Wash the combined solvent hexane extracts with 50-ml. portions of water until the last portion shows no pink color on the addition of phenolphthalein T.S. Allow the washed extract to stand for 5 minutes, discard any water that separates, and transfer the extract to a 300-ml. tall form beaker containing about 5 g. of anhydrous sodium sulfate. Stir for 2 minutes, and decant the solution into a 500-ml., tall-form beaker. Rinse the sodium sulfate with four 25-ml. portions of *Solvent Hexane*, combining the rinsings with the original extract. Reduce the total volume to about 30 ml. by evaporation on a steam bath, and transfer the concentrate to a small, round-bottom evaporation flask. Rinse the beaker with four 5-ml. portions of *Solvent Hexane*, adding the rinsings to the flask. With the aid of vacuum in a water bath at a temperature not exceeding 40°, or with a stream of nitrogen at room temperature, remove the remaining solvent completely. Dissolve the residue in a small amount of *Solvent Hexane*, transfer to a 10-ml. volumetric flask, and dilute with *Solvent Hexane* to volume to obtain the *Sample Preparation*

Procedure—

First Column Chromatography—Just as the 2 ml. of isooctane disappears into the surface of the prepared *First Column*, pipet 2.0 ml. of the *Sample Preparation* onto the column. As the meniscus of the *Sample Preparation* reaches the column surface, add the first of three 2-ml. portions of *Solvent Hexane*, adding each succeeding portion as the preceding portion disappears into the column. Continue adding *Solvent Hexane* in portions of 5 to 10 ml. until 100 ml. has been added. If necessary, adjust the flow rate to between 3 and 6 ml. per minute, by application of gentle pressure at the top of the chromatographic tube.

Discard the first 20 ml. of effluent, and collect the remainder. Examine the column under ultraviolet light at intervals during the chromatography, and stop the flow when the front of the fluorescent band representing vitamin A is about 5 mm. from the bottom of the column. (The ultraviolet lamp should provide *weak* radiation in the 300-mμ region. It is frequently necessary to use a narrow aperture or screen with commercial lamps to reduce the amount of radiation to the minimum required to visualize the vitamin A on the column.)

Transfer the eluate to a suitable evaporation flask, and remove the solvent hexane completely under vacuum at a temperature not above 40°, or with a stream of nitrogen at room temperature. Dissolve the residue in about 10 ml. of *Solvent Hexane*.

Second Column Chromatography—Add the solvent hexane solution obtained as directed under *First Column Chromatography* onto the *Second Column*. Rinse the evaporation flask with a total of 10 ml of solvent hexane in small portions, adding each portion to the *Second Column* and allowing it to flow through the column, and discard the effluent. When about 1 ml. of the solvent hexane remains above the surface of the column, add 75 ml. of benzene, and elute with the aid of gentle suction (about 125 mm. of mercury), collecting the eluate. Evaporate the benzene under vacuum at a temperature not above 40°, or with a stream of nitrogen at room temperature.

Assay Preparation—Dissolve the residue obtained as directed under *Second Column Chromatography* in a small amount of *Ethylene Dichloride*, transfer to a 10-ml. volumetric flask, and dilute to volume with *Ethylene Dichloride* to obtain the *Assay Preparation*.

Color Development—Into each of three suitable, matched colorimeter tubes of about 2-cm. diameter, and designated *1*, *2*, and *3*, respectively, pipet 1.0 ml. of the *Assay Preparation*. Into tube *1* pipet 1.0 ml. of the *Standard Preparation*, into tube *2*, 1.0 ml. of *Ethylene Dichloride*, and into tube *3*, 1.0 ml. of a mixture of equal volumes of acetic anhydride and *Ethylene Dichloride*. To each tube add quickly, and preferably from an automatic pipet, 5.0

ml. of *Color Reagent*, and mix. Exactly 45 seconds after the addition of the color reagent, determine the absorbances of the three solutions at 500 mμ, with a suitable spectrophotometer, using *Ethylene Dichloride* as the blank. Similarly, 15 seconds after making the first reading on each solution, determine the absorbances of the solutions in tubes 2 and 3 at 550 mμ, in a similar manner. Designate the absorbances as A^1_{500}, A^2_{500}, A^3_{500}, A^2_{550}, and A^3_{550}, respectively, in which the superscript indicates the number of the tube and the subscript the wavelength.

Calculation—Calculate the quantity, in mcg., of vitamin D in the portion of the sample taken by the formula $(C_S/C) \times (A_U/A_S)$, in which C_S is the concentration of vitamin D in mcg. per ml. of the *Standard Preparation*, C is the concentration of the sample (as g., capsules, tablets, etc.) in each ml. of the final solution, A_U has the value of $(A^2_{500} - A^3_{500}) - 0.67(A^2_{550} - A^3_{550})$ determined from the absorbances observed on the solution from the *Assay Preparation*, and A_S has the value of $A^2_{550} - A^3_{500}$ determined on the solution from the *Standard Preparation*.

VOLUMETRIC APPARATUS

Most of the volumetric apparatus available in the United States is calibrated at 20°, although the temperatures generally prevailing in laboratories more nearly approach 25°, which is the temperature specified generally for National Formulary tests and assays. This discrepancy is inconsequential provided the room temperature is reasonably constant and the apparatus has been calibrated accurately prior to and under the conditions of its intended use.

Use—To attain the degree of precision required in many NF assays involving volumetric measurements and directing that a quantity be "accurately measured," the apparatus must be chosen and used with exceptional care. Where less than 10 ml. of titrant is to be measured, a 10-ml. buret or microburet generally is required.

The design of volumetric apparatus is an important factor in assuring accuracy. For example, the length of the graduated portions of graduated cylinders should be not less than five times the inside diameter, and the tips of burets should permit an outflow rate of not more than 0.5 ml. per second.

Standards of Accuracy—The capacity tolerances for volumetric flasks, transfer pipets, and burets are those accepted by the National Bureau of Standards,* as indicated in the accompanying tables.

The capacity tolerances for measuring (*i.e.*, "graduated") pipets of up to and including 10-ml. capacity are somewhat larger than those for the corresponding sizes of transfer pipets, namely, 10, 20, and 30 μl. for the 2, 5, and 10-ml. sizes, respectively.

Transfer and measuring pipets calibrated "to deliver" should be drained in a vertical position and then touched against the wall of the receiving vessel to drain the tips. Volume readings on burets should be estimated to the nearest 10 μl. for 25 and 50-ml. burets, and to the nearest 5 μl. for 5 and 10-ml. burets. Pipets calibrated "to contain" are called for in special cases, generally for measuring viscous fluids like syrups. In such cases, the pipet should be washed clean, after draining, and the washing added to the measured portion.

* See "Testing of Glass Volumetric Apparatus," NBS Circ. 602, April 1, 1959.

Volumetric Flasks

Designated volume, ml.	10	25	50	100	250	500	1000
Limit of error, ml.	0.02	0.03	0.05	0.08	0.12	0.15	0.30
Limit of error, percent	0.20	0.12	0.10	0.08	0.05	0.03	0.03

Transfer Pipets

Designated volume, ml.	1	2	5	10	25	50	100
Limit of error, ml.	0.006	0.006	0.01	0.02	0.03	0.05	0.08
Limit of error, percent	0.60	0.30	0.20	0.20	0.12	0.10	0.08

Burets

Designated volume, ml.	10 ("micro" type)	25	50
Subdivisions, ml.	0.02	0.10	0.10
Limit of error, ml.	0.02	0.03	0.05

EXCERPT FROM PLAINTIFFS' SUPPLEMENTAL MEMORANDUM RESPONDING TO QUESTION OF DISTRICT COURT

IV.

A. Plaintiff Solgar Co., Inc.: The $50,000 cost for relabelling and reformulation constitutes approximately 14 percent of the company's operating expenses and approximately one-third of its net profits.

B. Leeds-Dixon Laboratories, Inc.: The $75,000 expenditure on the part of said company constitutes approximately 8 percent of its operating expenses.

C. Solgar Co., Inc. sells the following dosage forms of vitamins A and D:

Vitamin A - 5,000 IU, 10,000 IU, 25,000 IU.
Vitamin D - 400 IU, 1,000 IU, 2,000 IU, 2,500 IU.

D. Leeds-Dixon Laboratories, Inc. sells the following dosage forms of vitamins A and D:

Vitamin A - 5,000 IU, 10,000 IU, 12,500 IU, 15,000 IU, 25,000 IU.

Vitamin D - 400 IU. Lower dosages are found naturally in various foods.

NLR:vk

AFFIDAVIT OF NAOMI L. REICE
(Filed September 20, 1973)

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO, INC.,

Plaintiffs,

-against-

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

AFFIDAVIT

73 Civ. 3448 (MEF)

STATE OF NEW YORK)
COUNTY OF NEW YORK : ss.:
SOUTHERN DISTRICT OF NEW YORK)

NAOMI L. REICE, being duly sworn, deposes and says:

1. I am an Assistant United States Attorney in the office of Paul J. Curran, the United States Attorney for the Southern District of New York, attorney for defendants. I submit this affidavit to set forth for the Court certain information which has been furnished to this office by the Public Health Service of the Food and Drug Administration. The letters accompanying the transmission of the information are annexed hereto as Exhibits A and B.

2. The information contained in this affidavit relates to certain statements contained in Part IV. of plaintiffs' Supplemental Memorandum about the operations of plaintiff Solgar Co., Inc. ("Solgar") and Leeds-Dixon Laboratories, Inc., ("Leeds-Dixon") which markets its products under the "Schiff" Label.

3. In Point IV of plaintiffs' memorandum it is stated that Solgar sells Vitamin A is the following dosage units: 5,000 IU, 10,000 IU and 25,000 IU. Annexed hereto as Exhibit C is a label of Solgar which reflects a 50,000 unit

NLR:vk

vitamin A capsule among its product line.

4. Annexed hereto as Exhibit D is Solgar's label for a product called "Super-Plex" for which Solgar suggests a dosage of 3 to 6 tablets daily. If six tablets are consumed, 30,000 units of Vitamin A are ingested.

5. As to Leed-Dixon, plaintiffs informed the Court that it sells Vitamin D in units of 400 IU. On page 13 of Leeds-Dixon's (Schiff's) catalogue is listing for "Halibut Liver Oil Capsules" represented as containing 850 units of Vitamin D. See Exhibit E.

6. Moreover, if a consumer takes Leeds-Dixon's "Gerimost" tablets as directed, See Exhibit F, page 10 of catalogue, a consumer would ingest 1,000 units of vitamin D.

7. It is recognized that the information contained in this affidavit is not absolutely current, but it is the latest information on file with the FDA and, if still accurate, highly relevant.

s/
NAOMI L. REICE
Assistant United States Attorney

Sworn to before me
this 19th day of September

[illegible]

Notary Public

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CABLE ADDRESS: NYFOODRUG

NEW YORK DISTRICT
850 THIRD AVENUE
BROOKLYN, NEW YORK 11232
TELEPHONE: (212) 788-5000

Honorable Paul J. Curran
United States Attorney
Southern District of New York
United States Court House
Foley Square
New York, New York 10007

Attention: Naomi L. Reice
Ass't U.S. Attorney

Re: Solgar Co., Inc.
New York, New York

Dear Madam:

Pursuant to a request from Mr. Steve McNamara of the General Counsel's office of the U.S. Food and Drug Administration on 9/14/73, please be advised that the New York District office of the U.S. Food and Drug Administration conducted an inspection at the above referenced firm which was completed on August 8, 1971. It was determined at that time that Solgar Company was a manufacturer, repacker and relabeler of a long line of vitamin products marketed under their name.

Enclosed are examples of labels of vitamin A and vitamin D containing products that were collected during that inspection.

We would appreciate you returning the labels to this office when you have finished with them.

Yours truly,

TED M. HOPES
Acting Director
Compliance Branch
New York District

/jpb

EXHIBIT A

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

NEWARK DISTRICT
ROOM 831 - 970 BROAD STREET
NEWARK, NEW JERSEY 07102
TELEPHONE: 201-645-2344

September 14, 1973

Honorable Paul J. Curran
U.S. Attorney for the Southern
District of New York
U.S. Court House, Foley Square
New York, N.Y. 10007
c/o A.U.S.A. Naomi L. Reice

Dear Sir,

RE: Leeds-Dixon Laboratories Corp.
Moonachie, New Jersey

Pursuant to a request from Mr. Steve McNamara of the General Counsel's office of the U.S. Food and Drug Administration on 9/14/73, please be advised that the Newark District office of the U.S. Food & Drug Administration conducted an inspection at the above referenced firm which was completed on 6/23/72. It was determined at that time that Leeds-Dixon Laboratories manufactures a long line of vitamin preparations and packages them under the "Schiff Bio-foods product Inc." label. These vitamin preparations are the firm's main line of dietary supplements.

Enclosed is a catalogue of Schiff products obtained during the inspection at Leeds-Dixon Laboratories, Moonachie, N.J., which shows that most of the products are offered under the "Schiff" label.

We would appreciate your returning the catalogue to this office upon completion of your use.

George Troublefield
Acting Director Compliance Branch
Newark District

GT/dj

Enclosure

EXHIBIT B

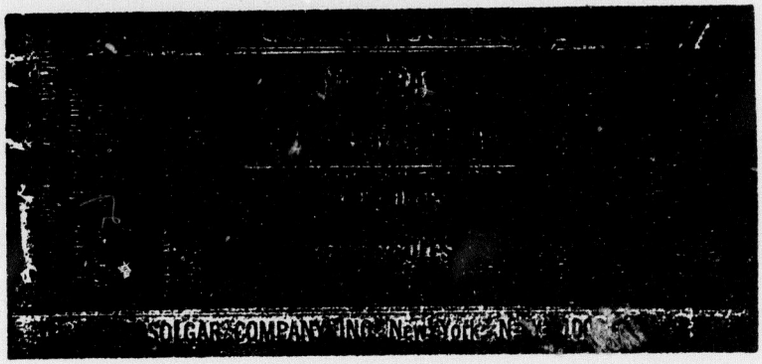


EXHIBIT C

BEST COPY AVAILABLE

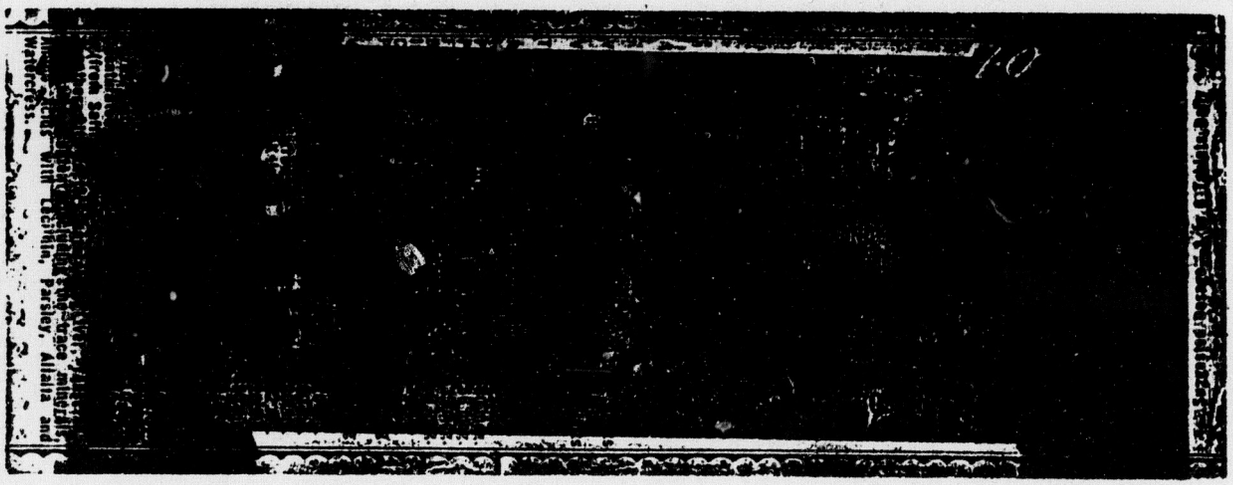


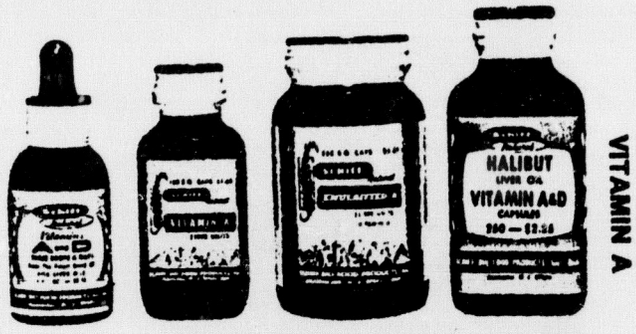
EXHIBIT D

ALL-NATURAL VITAMIN CATALOG AND DIGEST

VOL. 12 NO. 1

QUALITY Schiff NATURAL

EMULSIFIED A CAPS/HALIBUT LIVER OIL CAPS
VITAMIN A CAPS/A-D DROPS



VITAMIN A

Emulsified A Capsules

For Greater Digestibility

Livers from the freshest fish available, a pectin emulsifier to reduce the size of the fat globules—and you get the perfect, most digestible Vitamin A supplement. 25,000 unit capsules.

EMULSIFIED A Capsules		
100	250	500
$1.95	$4.35	$7.95

Halibut Liver Oil Capsules

Natural Vitamin A in Tiny 3 Minim Capsules!

"Gourmet" health preferences? Get your Vitamin A as well as 850 units of Vitamin D from the livers of fresh halibut. 5,000 units Vitamin A and 850 units Vitamin D.

HALIBUT LIVER OIL Capsules	
100	250
$1.00	$2.25

Vitamin A Capsules

Many Oils in One Capsule

Our "perles" of health, derived from a potpourri of the finest deep-sea fish, and swallowed with the greatest of ease. 25,000 unit caps.

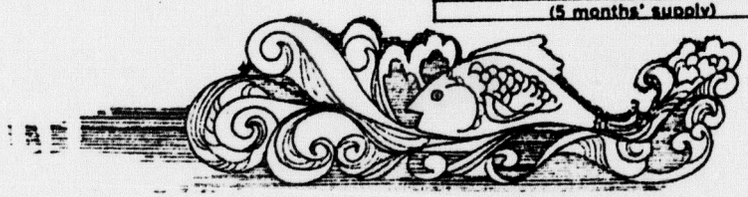
VITAMIN A Capsules		
100	250	1,000
$1.65	$3.75	$14.00

A-D Drops

5,000 Units of A in Only 3 Drops

Add 500 units of Vitamin D and you have 125% of the MDR for both Vitamins A and D. All this in only 3 drops daily and no need to swallow capsules. One bottle contains 450 drops distilled from the finest fish liver oils.

A-D DROPS
1 oz.
$2.50
(5 months' supply)



GERIMOST For the Mature
NUCLE-BEC

Gerimost

Schiff Has Designed A High Potency Vitamin-Mineral-Enzyme Formula Specifically for the Mature in Easy to Take Dosage Form

The step slows a little, interest in daily living may lag, preparing food and eating become a chore, some foods are not tolerated as well as before. This is the story of too many people who face maturity.

And so the dietary intake suffers, the step becomes even slower, and interest in daily activity wanes. But many mature people have discovered that this need not be. They have learned how to break the negative cycle, by following Schiff's healthful regimen: ample sleep, avoiding stress, exercise and sensible nutrition. For only when the diet is complete with essential nutrients, can the negative cycle be broken.

GERIMOST, the quality formula for the mature, that offers all these features:

■ Two piece capsule; ■ More Vitamin E from unesterified tocopherols; ■ More iron; ■ More pancreatic enzymes; ■ More soluble bioflavonoids; ■ Instant dissolvability for greater absorbability; ■ Easily swallowed; ■ May be easily opened to mix into food.

GERIMOST Capsules		
90	180*	360
$4.25	$7.90	$14.50

*month's supply

GERIMOST ANALYSIS
2 capsules with each meal (6 daily)

NATURAL VITAMINS	
Vitamin A	25,000 USP Units
Vitamin D	1,000 USP Units
Vitamin B-1	7 mg.
Vitamin B-2	14 mg.
Vitamin C	200 mg.
Niacin	4.50 mg.
Cobalamin (B-12 Activity)	25 mcg.
Vitamin E (d-alpha)	100 Int. Units
Bioflavonoids (water soluble) plus Hesperidin, Rutin	40 mg.
NATURAL MINERALS	
Calcium	550 mg.
Phosphorus	200 mg.
Iron	40 mg.
Iodine	0.1 mg.
Magnesium	40 mg.
ENZYMES	
Natural Enzymes From Pancreas	
Protease, Diastatic, Lipolytic	100 mg.
Pepsin	50 mg.
Plus many other natural food factors:	
Glutamic Acid	75 mg.
Nucleic Acid	75 mg.

Nucle-BEC

Nucleic Acid Fortified with Three Important Vitamins B, E and C.

You have probably read about the interesting research which is being conducted on Nucleic Acid. Now Schiff brings you Nucle-BEC, a substantial Nucleic Acid formula.

In addition to 100 mg. of Nucleic Acid, Schiff Nucle-BEC is fortified with large amounts of 6 more nutrients — all essential to your system. You get 4 of the most important B Vitamins; plus over 3 times the MDR of Rose Hips C, plus 50 I.U. of Vitamin E. All natural.

NUCLE-BEC Tablets		
60	120	240
$3.25	$5.75	$9.50

EXHIBIT F

OPINION OF DISTRICT COURT
DENYING PLAINTIFFS' MOTION FOR A PRELIMINARY INJUNCTION
(Filed September 25, 1973)

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,	:	
Plaintiffs,	:	
-against-	:	
CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,	:	MEMORANDUM
	:	73 Civ. 3448
Defendants.	:	

FRANKEL, D.J.

On October 1, 1973, regulations of the Food and Drug Administration will become effective requiring that preparations of Vitamin A and Vitamin D in excess of 10,000 I.U. (international units) per dosage unit and 400 I.U. per dosage unit, respectively, shall be restricted to prescription sale and that such vitamins shall be labelled accordingly. The regulations read as follows:

21 C.F.R. §3.94

"(a) Vitamin A is an essential nutrient for humans. It is widely recognized that large amounts of vitamin A can cause adverse effects, some of which are serious. The U.S. Recommended Daily Allowance (U.S. RDA) for vitamin A is 1500 International Units, (IU) for infants, 2500 IU for children under 4 years of age, 5000 IU for adults and children 4 or more years of age, and 8000 IU for pregnant or lactating women.

"(b) In view of the toxicity of excessive consumption of vitamin A, the Food and Drug Administration finds that, in order to protect the public health, oral preparations containing vitamin A in excess of 10,000 IU per dosage unit or recommended daily intake are drugs subject to section 503 (b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

"(1) The label bears the legend. 'Caution: Federal law prohibits dispensing without a prescription'; and

"(2) The labeling bears full disclosure information as required by §1.106(b)(3)(i) of this chapter, and especially appropriate warnings regarding vitamin A toxicity.

"(c) Preparations containing 10,000 or less IU of vitamin A per dosage unit will be regarded as misbranded if their recommended daily intake exceeds 10,000 IU."

'21 C.F.R. §3.95

"(a) Vitamin D is an essential nutrient for humans. It is widely recognized that vitamin D, when ingested daily in large amounts, is toxic. The U.S. Recommended Daily Allowance (U.S. RDA) for vitamin D is 400 International Units (IU).

"(b) In view of the toxicity of the excessive consumption of vitamin D, the Food and Drug Administration finds that, in order to protect the public health, oral preparations containing vitamin D in excess of 400 IU per dosage unit or recommended daily intake are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

"(1) The label bears the legend, 'Caution: Federal law prohibits dispensing without a prescription'; and

"(2) The labeling bears full disclosure information as required by §1.106(b)(3)(i) of this chapter, and especially appropriate warnings regarding vitamin D toxicity.

"(c) Preparations containing 400 or less IU of vitamin D per dosage unit will be regarded as misbranded if their recommended daily intake exceeds 400 IU.

"(d) Foods which are represented for use solely under medical supervision to meet nutritional requirements of persons with poor vitamin D absorption may contain vitamin D not in excess of 1000 IU per dosage unit or recommended daily intake."

[redacted]

This is an action charging that the quoted regulations are invalid and seeking to enjoin their enforcement. The plaintiffs have moved for a preliminary injunction. The extraordinary relief thus sought must be denied upon the findings of fact and conclusions of law outlined below.

The plaintiffs are the National Nutritional Foods Association, a trade association composed of manufacturers, wholesalers, and retailers of vitamins and dietary supplements, and Solgar Co., Inc., a New York corporation which manufactures, distributes, and sells vitamin supplements.

The immediate background of the regulations in question begins with their promulgation by the Commissioner of Food and Drugs as proposed regulations in the Federal Register dated December 19, 1972 (37 Fed. Reg. 26618). These regulations were corrected in minor detail in the Federal Register dated January 4, 1973 (38 Fed. Reg. 799). The Commissioner promulgated these regulations for the "efficient enforcement"

of §§502(a), (f), and (j), and 503(b) of the Food and Drug Act as authorized by 21 U.S.C. §371(a), under powers delegated to him by the Secretary. 21 C.F.R. §2.120.

Explaining what were then his tentative views, the Commissioner said:

> "The acute and chronic toxicity of these vitamins is documented extensively in the medical literature. Vitamin A is available over the counter in dosage levels up to 10 times the recommended daily dietary allowance (RDA) of the Food and Nutrition Board, National Academy of Sciences-National Research Council (NAS-NRC) and vitamin D is available up to 60 times the RDA. The availability without prescription of these vitamins in high dosage levels contributes significantly to their misuse and the occurrence of serious adverse effects." (37 Fed. Reg. 26618 (1972)).

Adverse effects which the Commissioner found from excessive intake of Vitamin A include among others anorexia, growth retardation in children, migratory arthralgia and intracranial pressure. Adverse effects resulting from an excess of Vitamin D include anorexia, weight loss, polyuria, certain forms of calcification, hypertension, anemia, irreversible renal failure and death. In respect of

Vitamin D the Commissioner noted that some of these severe effects are irreversible, and that the margin of safety between nutritional requirements and toxic levels is small.

An extensive bibliography listing the scientific articles used by the FDA in formulating its proposed regulation was placed on public view.

When the Commissioner published the proposed rules and their rationale he provided 60 days in which interested parties might comment, in accordance with the rulemaking provisions of the Administrative Procedure Act. (5 U.S.C. §553(c)). The response was massive. Over 2500 comments were received. Of special interest for present purposes, the two plaintiffs herein, as well as other drug companies, presented substantial amounts of factual material and expert opinion opposing the proposed regulations. Others made extensive submissions pro and con. The mass of these presentations has been lodged with the court and fills some 45 manila folders.

The commentators, responding to the Commissioner's invitation, fell into three general categories:

(1) Those who agreed that prescription levels are necessary and that those proposed by the FDA were suitable. This group included official representatives of the American Academy of Pediatrics, the American Medical Association, the American Dietetic Association, and other medical and scientific experts.[1]

(2) Those who agreed that prescription levels were necessary but argued that the levels should be higher than those set by the FDA. These groups included most drug manufacturers and trade associations as well as a few individual consumers.

---

1. One group of commentators, mainly scientists and medical researchers, argued that the Commissioner should actually set lower unit limits for prescription sales.

Several of these commentators made a critical review of the scientific literature used by the FDA, arguing generally that "toxicity below 50,000 I.U. daily for vitamin A was rare and that vitamin D toxicity reports would not support the vitamin D level proposed." (38 Fed. Reg. 20724 (1973)).

(3) Those who disagreed with the proposal entirely, arguing that vitamins are foods and that individuals should have the right to use any amounts they desire. Most individual consumer comments as well as comments from health food retailers fell in this category. Such commentators pointed out that the dosage level of vitamins in many foods is higher than the prescription level - for example, 100 grams of liver contains at least 24,000 I.U. of vitamin A - and that a limitation on vitamins and not on food substances is irrational.

Having considered the factual and legal materials submitted for his expert judgment, the Commissioner concluded that the regulations now assailed should be adopted. (38 Fed. Reg. 20723 (1973)).

As grounds for this determination he noted that:

> "The concern of the Food and Drug Administration is the availability of vitamin A and vitamin D in large dosage units in medicinal forms, i.e., capsules and tablets, particularly in view of the multiplicity of other sources of this vitamin in the daily diet. The convenience of ingestion in this form on a routine basis encourages excessive intake of these vitamins far beyond the average amounts ingested in normal diets of conventional food over extended periods of time. Adequate amounts of vitamin A and vitamin D will continue to be available as dietary supplements and are not being removed from the market place. The margins of safety provided in the levels established by this proposal were developed to take into account the wide ranges of vitamin content in foods and the dosage levels of vitamin A and vitamin D preparations that are usually implicated in toxic conditions." (38 Fed. Reg. 20724 (1973)).

Aiming to establish a reasonable "margin of safety," the Commissioner concluded that the limits he had proposed were prudent and efficacious.

In support of their claim that the Commissioner's regulations are not valid - and, more immediately, that the invalidity and resulting injury are clear enough to warrant the extraordinary relief of a preliminary injunction - the plaintiffs argue that:

(1) The Commissioner has exceeded his statutory authority in that he has improperly classified vitamins as drugs when they are in fact food substances and beyond the range of the Commissioner's authority to regulate.

(2) In any case vitamins, even if classified as drugs, cannot be defined as a "prescription drug" within the ambit of 21 U.S.C. §353, which these regulations are designed to effectuate.

(3) The Commissioner's decision to require prescription limitations for vitamin A and D is not supported by the medical and scientific evidence and is factually unreasonable.

None of these claims can be sustained.

(1) Plaintiffs argue that vitamins are food substances and thus not subject to FDA regulations as "drugs." The Commissioner has made the judgment, however, that vitamins are a food only when used within the limits of the recommended daily allowance. At such a level they, like ordinary foods, are "nutrients." Above those levels they are deemed "appropriate only for therapeutic purposes and thus are properly classified as drugs" (38 Fed. Reg.

20723 (1973)).

21 U.S.C. §321(g)(1) defines the term "drug" as follows:

> "(A) articles recognized in the official United States Pharmacopeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clauses (A), (B), or (C) of this paragraph; but does not include devices or their components, parts, or accessories."

This language is to be construed liberally in the light of the statutory concern for health and safety. See, e.g., United States v. Bacto-Unidisk, 394 U.S. 784, 792 (1969); United States v. Sullivan, 332 U.S. 689, 693-97 (1948); United States v. Dotterweich, 320 U.S. 277, 280 (1943); United States v. Diapulse Corporation of America, 457 F.2d 25, 28 (2d Cir. 1972). Quite apart from rules of construction, and leaving aside the lay knowledge that the likeliest place to go for vitamins is the "drug store," the

products here are squarely within the literal language and evident meaning of the statute. If there were more doubt, the question would surely be one on which to weigh further against plaintiffs the everyday experience and judgmental responsibility of the Commissioner. N.L.R.B. v. Hearst Publications, 322 U.S. 111, 130 (1944).

(2) Plaintiffs argue that even if Vitamins A and D are to be denominated "drugs," they do not fall within the statutory definition of a "prescription drug" subject to the kind of regulatory authority the Commissioner has asserted. The provision in question is 21 U.S.C. §353, which states in relevant part:

> "(b)(1) A drug intended for use by man which—
>
> * * *
>
> "(E) because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug
>
> * * *
>
> shall be dispensed * * * upon * * * prescription * * *."

It is plain that the concern over "potentiality for harmful effect" imposes broad responsibility upon the Commissioner to safeguard human health. He has acted well within that duty in setting upper limits at a level convenient and agreeable for affected consumers (including those who may want two or three pills to reach levels recommended by the most exuberant of vitamin enthusiasts) while affording protection through a safety margin against dangers which have been universally acknowledged even if they are not mechanically quantifiable at a precisely agreed level. The Commissioner is not only entitled but required to be at least as prudent as lay understanding of human behavior would dictate. He knows that almost nobody has a reliably identified need for as much as - let alone more than - 10,000 daily units of Vitamin A.[2]

2. Comparable observations apply to Vitamin D.

He knows, because we all do, of the prevalent wisdom among us pill swillers that "if one is good, two are better." He knows such things as the widely held belief in the efficacy of Vitamin A for acne, and he knows that moderation may not be the chief attibute of those troubled by this condition. Knowing such obvious things and other matters less patent, the Commissioner is not required to circumscribe his reponsibilities in terms solely of the completely "rational" consumer. He may and he must consider the "potentiality for harmful effect" through excessive use to the merely "average" man and even to the substantial numbers of us who help create the average by falling below it.

Both plaintiffs and defendants agree that toxicity exists at some level. Plaintiffs' quarrel with the Commissioner is over the dosage point at which some restrictions would become prudent. The Commissioner, however, is not required to set the over-the-counter limit at a maximum which the consumer (be he old, young, weak or strong) might withstand. See United States v. Rodine Products, 206 F. Supp. 201, 207 (D.Ariz. 1962).

A substantial margin of safety probably should - certainly may - be used, at least in a case like this, where it can have only beneficial effects for the Commissioner's paramount subject of health.

> "One making a rule for the future which in practical effect will determine whether millions of people shall eat something everyday may reasonably refuse to subject the general public to even slight risks and small deceptions." Atlas Powder v. Ewing, 201 F.2d 347, 355 (3d Cir. 1952).

(3) Plaintiffs launch a variety of procedural and "evidentiary" attacks upon the factual premises of the regulations. None of these seems meritorious.

The Commissioner's judgments about safety levels (in the admittedly uncertain and debated state of knowledge) and consumer habits are solidly grounded. If the question were for de novo decision, the court would probably decide as he did. But it is enough to say his determinations are reasonable and rational.

Though they had ample opportunity to present anything pertinent to the FDA, plaintiffs urge that they should be permitted to make a new record here, presumably to show that the Commissioner must be denounced as

"arbitrary and capricious" on the basis of materials he was not invited to look at. The argument would appear to lack merit, but it need not be resolved finally for present purposes. Moving with the relative dispatch required by the occasion, the court has considered all the materials submitted, including those the Commissioner was not given. The result remains that the rationality of the questioned regulations unquestionably survives the effort to block them by a preliminary injunction.

The balance of the equities is heavily against the plaintiffs. They have offered some unimpressive figures for the expense of relabeling their vitamin bottles and putting up new pill strengths - for all of which the Commissioner gave long notice before the effective date of his regulations. Informed that the figures were vague and unenlightening, plaintiffs expanded the alleged numbers in a brief. The result remains less than imposing.

If people want 20,000 or 30,000 units of Vitamin A, they can dose themselves with two or three pills - or, better still, see a doctor first.

As the court has attempted to indicate, this sort of mild obstacle to the swallowing of toxic amounts seems compellingly sensible - a quality not necessarily objectionable for regulatory decisions.

In short, the public interest in health quite overwhelms the financial concerns plaintiffs urge.

Beyond that, the likelihood that plaintiffs will succeed in this action seems negligible.

There are, then, no grounds for, and powerful grounds against, a preliminary injunction.

Plaintiffs' motion is denied. So ordered.

Dated: New York, New York
September 25, 1973

Marvin E. Frankel
U.S.D.J.

UNITED STATES COURT OF APPEALS

FOR THE SECOND CIRCUIT

No. 439 - September Term, 1973

(Argued October 19, 1973 Decided November 2, 1973)

Docket No. 73-2430

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,

Plaintiffs-Appellants,

v.

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Foods and Drugs,

Defendants-Appellees.

BEFORE:

MEDINA, LUMBARD and TIMBERS, Circuit Judges.

Appeal from an order entered in the Southern District of New York by Marvin E. Frankel, District Judge, which denied appellants' motion for a preliminary injunction to enjoin from becoming effective certain regulations of the Food and Drug Administration concerning Vitamins A and D.

Affirmed.

Milton A. Bass, New York, N.Y. (Bass & Ullman, New York, N.Y., on the brief), for plaintiffs-appellants.

Naomi L. Reice, Asst. U.S. Atty., New York, N.Y. (Paul J. Curran, U.S. Atty., and John W. Nields, Jr., Asst. U.S. Atty., on the brief), for defendants-appellees.

PER CURIAM:

The sole issue on this appeal from an order entered September 25, 1973 in the Southern District of New York by Marvin E. Frankel, District Judge, which denied plaintiffs' motion for a preliminary injunction to enjoin regulations of the Food and Drug Administration concerning Vitamins A and D from becoming effective, is whether, under the well established standards in this Circuit applicable to the extraordinary remedy of a preliminary injunction, the district court abused its discretion in denying it. We affirm.

Appellants are the National Nutritional Foods Association, a trade association of manufacturers, wholesalers and retailers of vitamins and dietary supplements, and Solgar, Co., Inc., a manufacturer, distributor and seller of vitamin supplements. Appellees are the Secretary of HEW and the Commissioner of Foods and Drugs.

On December 19, 1972, the Commissioner proposed, by publishing in the Federal Register, certain regulations of the Food and Drug Administration requiring that preparations of Vitamin A and Vitamin D in excess of 10,000 I.U. (international units) per dosage unit and 400 I.U. per dosage unit, respectively, be restricted to prescription sale and that such vitamins be labelled accordingly. 37 Fed. Reg. 26618 (1972), as amended, 38 Fed. Reg. 799 (1973). The regulations were proposed to implement the "efficient enforcement" of Sections 502(a), (f) and (j) and 503(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§352(a), (f) and (j) and 353(b)(1970), as authorized by 21 U.S.C. §371(a)(1970), and pursuant to powers delegated to the Commissioner by 21 C.F.R. §2.120(a)(1)(1973).

Consideration of the proposed regulations followed standard rule making procedure prescribed by the Administrative Procedure

NPI-Sandstone
4-23-71—100M—8046

Act, 5 U.S.C. §553 (1970), including requirements as to notice and public participation. Among the 2500 comments received in response to the Commissioner's invitation were comments from the two appellants herein, each of which submitted voluminous factual material and expert opinions opposing the proposed regulations. After due consideration, the Commissioner concluded that the regulations should be adopted. Accordingly, they were promulgated on July 25, 1973, to become effective October 1, 1973. 38 Fed. Reg. 20723, 20725 (1973).

Having failed to dissuade the Commissioner from promulgating the regulations, appellants on August 6, 1973 commenced the instant action in the Southern District of New York seeking declaratory and injunctive relief. Jurisdiction was invoked pursuant to 28 U.S.C. §1331(a) (1970). A week later, appellants filed their motion for a preliminary injunction which Judge Frankel denied on September 25, 1973 in an opinion setting forth his findings of fact and conclusions of law. On September 26, we ordered an expedited appeal and heard it on October 19.

Our careful examination of the record satisfies us that it fully supports the district court's denial of a preliminary injunction under the well established standards in this Circuit applicable to the extraordinary relief sought. See Gulf & Western Industries, Inc. v. Great Atlantic & Pacific Tea Company, Inc., 476 F.2d 687, 692-93 (2 Cir. 1973), and authorities there cited.

We affirm for the reasons stated in Judge Frankel's comprehensive opinion. ___ F.Supp. ___ (S.D.N.Y. 1973).

Affirmed.

BEST COPY AVAILABLE

NOTICE OF DEPOSITION
(Filed October 5, 1973)

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,

Plaintiffs,

vs.

CASPER W. WEINBERGER, Secretary of Health, Education & Welfare and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

73 Civ. 3448 (MEF)

NOTICE OF DEPOSITION UNDER F.R.C.P. 30(b)

S I R :

PLEASE TAKE NOTICE that pursuant to Rule 30(b) of the Federal Rules of Civil Procedure the deposition of defendant Alexander M. Schmidt, Commissioner of Food and Drugs and or such knowledgeable person or persons he may designate will be taken on oral examination at the offices of Bass & Ullman, Esqs., 342 Madison Avenue, New York, New York 10017, on Monday, October 15, 1973 at 10 o'clock A.M. and at any and all adjournments thereof.

The above named persons, whose depositions are being taken, are hereby notified to appear for said deposition and to bring with them any and all books, correspondence, records, medical reports and literature relating to their determination of the dosage levels of Vitamins A and D which are issue in the above entitled action.

Dated: New York, New York
October 5, 1973

Yours, etc.,

BASS & ULLMAN
Attorneys for Plaintiffs
Office & P.O. Address
342 Madison Avenue
New York, New York 10017
(212) 697-3880

TO: PAUL J. CURRAN, ESQ.
United States Attorney
Southern District of New York
Attorney for Defendants

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION, and SOLGAR CO., INC.,	:	
Plaintiffs,	:	
-against-	:	TEMPORARY RESTRAINING ORDER AND ORDER TO SHOW CAUSE
CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,	:	73 Civ. 3448 (MEF)
Defendants.	:	

Upon the annexed affidavit of Naomi L. Reice, Assistant United States Attorney, sworn to on October 11, 1973, and the exhibit attached hereto, it is hereby

ORDERED, that the plaintiffs, The National Nutritional Foods Association and Solgar Co., Inc., show cause before the Honorable Marvin E. Frankel, a Judge of this Court, at the United States Courthouse, Foley Square, New York, New York, in Room 2002, on the _____day of October, 1973, at _____o'clock in the _____noon, or as soon thereafter as counsel may be heard, why an order should not be entered pursuant to Rule 26(c) of the Federal Rules of Civil Procedure, vacating a notice of deposition directed to defendant Alexander M. Schmidt or his designee which plaintiffs have served upon defendants' attorney; and

MLR:be
73-2562

it is

ORDERED, that the plaintiffs are hereby restrained from taking the deposition of defendant Alexander M. Schmidt or his designee pending the hearing upon defendants' motion for a protective order; and it is further

ORDERED, that a copy of this order and all papers upon which it is based shall be served upon the office of the attorney for the plaintiffs on or before the _____day of October, 1973, at _____M.

Dated: New York, New York

October , 1973

_____

United States District Judge

MLR:bs
73-2562

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLAR CO., INC.,

Plaintiffs,

-against-

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

AFFIDAVIT

73 Civ. 3448 (MEF)

STATE OF NEW YORK)
COUNTY OF NEW YORK : ss.:
SOUTHERN DISTRICT OF NEW YORK)

NAOMI L. REICE, being duly sworn, deposes and says:

1. I am an Assistant United States Attorney in the office of Paul J. Curran, United States Attorney for the Southern District of New York, attorney for the defendant Alexander M. Schmidt, Commissioner of Food and Drugs, and as such I am in charge of and familiar with this action.

2. I make this affidavit in support of defendants' application for an order directing the plaintiffs in the action to show cause why an order should not be entered vacating a notice to take the deposition of defendant Schmidt or his designee which plaintiffs have served upon defendant's attorney. A copy of that notice is annexed

hereto as Exhibit A.

3. Defendants make this motion because in an action such as this, in which plaintiffs seek declaratory and injunctive relief to prevent the enforcement of duly issued regulations of an administrative agency, the Administrative Procedure Act and the cases thereunder, (which were cited by defendants in their Memorandum in Opposition to plaintiffs' Motion for a Preliminary Injunction, filed on September 10, 1973, at pages 18-19) directs that a court's review be based upon the administrative record. That administrative record has already been filed with this Court. Litigation affidavits, and likewise deposition testimony, are not part of the whole record to which the Administrative Procedure Act focuses the Court's attention. Accordingly, we submit that, in the absence of highly special or unusual circumstances which might make depositions appropriate in a case such as this, there are no matters relevant to this case which could be inquired into on deposition. The taking of Mr. Schmidt's deposition in these circumstances would be unduly burdensome and oppressive.

4. The reason why this application is made by order to show cause rather than ordinary notice of motion is that an ordinary motion would be returnable after the date noticed for the taking of Mr. Schmidt's deposition.

5. No prior application has been made for the relief requested herein.

WHEREFORE, your deponent respectfully requests that the order to show cause in support of which this affidavit has been submitted be signed and entered by this Court.

/s/
NAOMI L. REICH
Assistant United States Attorney

Sworn to before me this
11th day of October, 1973

Notary Public

WALTER G. BRANNON
Notary Public, State of New York
No. 24-0394500
Qualified in Kings County
Cert. filed in New York County
Term Expires March 30, 1975

6. At 3:25 P.M., I spoke to Milton Bass, Esq. counsel to plaintiffs and informed him of this order to show cause and its stay provision. Mr. Bass consented to the stay contained herein and requested that the motion be made returnable during the week of October 22, 1973, subsequent to oral argument before the Court of Appeals in this matter on October 19, 1973

AFFIDAVIT OF MILTON A. BASS IN OPPOSITION
(Filed October 25, 1973)

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,

Plaintiffs,

-against-

CASPER W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

73 Civ. 3448 (MEF)

AFFIDAVIT IN OPPOSITION TO DEFENDANTS' MOTION

STATE OF NEW YORK)
) SS.:
COUNTY OF NEW YORK)

MILTON A. BASS, being duly sworn, deposes and says:

I am a member of the firm of Bass & Ullman, attorneys for the plaintiffs herein and respectfully submit this affidavit in opposition to defendants' motion to vacate the notice of deposition directed to defendant Alexander M. Schmidt.

The defendants seek to vacate the notice of deposition of Alexander M. Schmidt on the ground that the court's review in the instant action is limited to the administrative record herein. The briefs of both parties have heretofore been submitted to the Court with respect to this question of law. At this time, plaintiffs merely wish to add that the basic issue, which is presented upon this motion and upon the defendants' motion to dismiss, is really a very narrow one. If the defendants had filed a complaint and instituted an action claiming that a product was covered by the prescription statute, then, and in such

event the defendants would have had to go forward and prove their case by proper and relevant evidence. The defendants are here arguing that merely by issuing an interpretive regulation they no longer have to meet this burden.

No hearing was ever conducted by the Agency. The Agency merely invited comments about its proposed regulation. The defendants have argued that they did not even have to invite comments for the purpose of issuing an interpretive regulation. The argument of the defendants is simply that they merely have to issue an interpretive regulation stating that a product is covered by the prescription statute and that automatically becomes the law without any right to a trial, including cross-examination of the defendants' witnesses.

The defendants' contention is most certainly a new and unique interpretation of the law and of due process. If the defendants are correct, they will no longer have to bring actions claiming violations of the statute, but need merely issue interpretive regulations. Plaintiffs respectfully submit that the defendants are in error.

For the reasons herein set forth and as set forth in plaintiffs' briefs heretofore submitted to the Court, it is respectfully submitted that the defendants' motion should be denied.

/S/
MILTON A. BASS

Sworn to before me this
24th day of October, 1973.

JACOB LAUFER
NOTARY PUBLIC, State of New York
No. 31-4502286
Qualified in New York County
Commission Expires March 30, 1975

to obtain judicial relief. Instead, they can, as have the plaintiffs in the instant case, bring an action for declaratory judgment anticipating enforcement by the agency for the purpose of obtaining a judicial determination as to the validity of the agency action. The Court in Abbott Laboratories did not change the law as to the burden of proof and the scope of judicial review.

By seeking to limit the scope of review by this Court, defendants are in effect proposing a new rule of law contrary to the specific legislative history of the prescription statute and destructive of basic principles of due process, as well as a frustration of the legitimate purpose of a declaratory judgment action.

4. Even if the Court adopts the new rule of law proposed by defendants as to the scope of review, plaintiffs respectfully submit that discovery proceedings are nevertheless appropriate and essential in the instant case. The Administrative Procedure Act expressly states:

> "In making the...determinations, the court shall review the whole record...." 5 U.S.C. §706 (emphasis added)

This requirement relates to a full review by the Court of the entire record on which the administrative agency based its decision. Anything less than the "whole record" is not sufficient for a proper decision as to the propriety of the action taken by the administrative agency.

5. Plaintiffs respectfully submit that the record filed by the Food and Drug Administration in this case is not the "whole record" which was before the agency in that there are,

SUPPLEMENTAL AFFIDAVIT OF MILTON A. BASS

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

(Filed December 26, 1973)

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,

Plaintiffs,

-against-

CASPER W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

73 Civ. 3448 (MEF)

SUPPLEMENTAL AFFIDAVIT IN OPPOSITION TO DEFENDANTS' MOTION TO VACATE NOTICE OF DEPOSITION.

STATE OF NEW YORK)
) SS.:
COUNTY OF NEW YORK)

MILTON A. BASS, being duly sworn, deposes and says:

1. I am a member of the firm of Bass & Ullman, attorneys for plaintiffs and I make this supplemental affidavit in opposition to the motion brought on by defendants by way of an order to show cause requesting this Court to vacate a notice of deposition served by plaintiffs.

2. On October 5, 1973, plaintiffs served a notice of the taking of the deposition of Alexander M. Schmidt, Commissioner of Food and Drugs or his knowledgeable designee, along with a request for the production of all relevant documents, for the purpose of determining the basis for the dosage levels established in the Vitamin A and D regulations. Defendants' motion to vacate said notice is based on their contention that this Court is limited to reviewing the administrative "record" filed by the

Food and Drug Administration for the purpose of determining whether the action of the Commissioner was "arbitrary and capricious." 5 U.S.C. §706(2)(A). The instant case involves consideration of a "policy statement" or interpretive regulation issued by the defendants. There has never been a hearing in this matter, nor has there been any opportunity for cross-examination of witnesses.

3. Plaintiffs contend that the defendants cannot accomplish a restriction on the scope of review by issuing an interpretive regulation or policy statement instead of proceeding by way of a seizure or injunction action as contemplated by the Federal Food, Drug, and Cosmetic Act. It is important to note that prior to the landmark decision in the Abbott Laboratories case such regulations and policy statements were not subject to pre-enforcement judicial review. Instead, they could only be challenged when and if an administrative agency sought to enforce such regulation or policy statement by way of a criminal or civil proceeding. In such proceedings, the administrative agency would have had the full burden of establishing the validity of their policy statement or interpretive regulation and the defendant would have had a full opportunity to cross-examine the agency witnesses and to present his own proof.

The decision in Abbott Laboratories held that the federal courts do have jurisdiction to entertain an action for a declaratory judgment for pre-enforcement relief. Thus, after the Food and Drug Administration issues a statement of policy or interpretive regulation, an affected party no longer has to await

at least, the following substantial omissions and inadequacies:

A. The regulations establish prescription limitations at levels of 10,000 I.U. and 400 I.U. for Vitamins A and D respectively. The record does not show how these levels were determined. The only support for the levels are conclusory statements without any explanation or analysis. There have been no findings that any specific levels of Vitamins A or D are toxic or have potentiality for harmful effect. Discovery is essential to ascertain the basis, if any, for the dosage levels established by defendants.

B. In his policy statement, the Commissioner makes the following statement:

> "Based on consultation with the most knowledgeable experts available, the Commissioner finds that the scientific consensus is that the proposed limits are appropriate at this time." 38 F.R. 20724, col. 2 (Aug. 2, 1973) (emphasis added)

None of these consultations are part of the record in this Court. There is no indication as to who these "most knowledgeable experts" are and there is nothing in the record which states the substance of their communications to the Commissioner. Discovery is most certainly essential to ascertain these facts which defendant expressly states comprised the basis for his decision.

C. The Commissioner relies on a bibliography of articles in the medical literature to support the

Vitamin A and D regulations. 37 F.R. 24618 (Dec. 14, 1972). He states that several comments submitted made "their own analysis of the bibliography." 38 F.R. 20724 (Aug. 2, 1973). There is nothing in the record which presents the analysis of the bibliography, if any, which was made by the Food and Drug Administration in connection with determining the levels established for Vitamins A and D. There has been no opportunity for cross-examination of witnesses to ascertain what scientific conclusions can properly be drawn from this bibliography.

D. The Commissioner states that above the levels specified in the regulations, Vitamins A and D are appropriate only for therapeutic purposes. 38 F.R. 20723, col. 3 (Aug. 2, 1973). This contention is essential for the Commissioner's position that the products are drugs. The record does not show what the therapeutic purposes for Vitamins A and D are above the levels set, nor how the Commissioner decided that such therapeutic purposes exist.

The Commissioner bases a finding that Vitamins A and D have no food value above 10,000 I.U. and 400 I.U. on other regulations promulgated by him in another context. 38 F.R. 20723, col. 1 (Aug. 2, 1973). These regulations were promulgated after a two year public hearing and the factual and legal conclusions in them are currently being challenged in the

Court of Appeals for the Second Circuit. As a result of this challenge, the Food and Drug Administration stayed the effectiveness of those regulations. 38 F.R. 29577 (Oct. 26, 1973). No part of the record in the other regulations is part of the record filed by the FDA in this Court. There is nothing in the record herein to support a factual determination that Vitamins A and D have no food value at the specified dosage levels.

E. In his policy statement, the Commissioner makes the following statement:

> "The margins of safety provided in the levels established by this proposal were developed to take into account the wide ranges of vitamin content in foods and the dosage levels of Vitamin A & D that are usually implicated in toxic conditions." 38 F.R. 20724, cols. 2-3 (Aug. 2, 1973).

There is nothing in the record herein which shows how this formulation of a margin of safety was accomplished.

F. In his policy statement, the Commissioner makes the following statement:

> "Comment was received that consumers would be able to ingest as many dosage units as they desired and therefore the proposed limits would have no effect. The Commissioner cannot agree with this concept. The Commissioner believes that most consumers will carefully consider the advisability of taking dosages in excess of suitable recommended dosages. Conscientious consumers will have a basis upon which to make a judgment as to their intake of these vitamins. The fact that a small

> number of consumers will abuse their health...is no reason to forego a reasonable regulation that will afford appropriate public health protection for the vast majority of the public." 38 F.R. 20725, col. 3 (Aug. 2, 1973).

This issue relates to the purpose of the prescription requirement for a product and similarly requires adequate cross-examination for proper review in this Court.

G. The Food and Drug Administration previously issued a notice in which they took the position that Vitamins A and D in dosages of 50,000 I.U. each were subject to a prescription requirement. 36 F.R. 16125 (Aug. 19, 1971). There is nothing in the record to explain what new information was received by the FDA to justify the drastic reduction from the earlier levels they attempted to establish.

H. Although the Commissioner recognizes a distinction between children and adults with respect to toxicity levels [37 F.R. 26619, col. 1 (Dec. 14, 1972)], the record is silent as to why the regulations do not contain such a distinction. See 38 F.R. 20724, col. 1 (Aug. 2, 1973) where the Commissioner notes but does not respond to this objection as to non-distinction between children and adults.

I. Under the statute there are two requirements for placing a drug on a prescription basis:

1. The product must be toxic or have a potentiality for harmful effect, and

2. As a result of the above it must not be safe for use except under the supervision of a physician.

See 21 U.S.C. §353(b)(2)(B)

There is nothing in the record to explain how the Commissioner determined that the second of the above requirements was complied with and that Vitamins A and D at the specified levels were not safe for use except under the supervision of a physician.

6. In support of the Vitamin A and D regulations, the defendant has referred to a series of articles and reports. No findings or statements have been made as to the scientific conclusions which can be drawn from these articles. Cross-examination is most essential in this area. We must ascertain what scientific and factual conclusions were made by the Commissioner as a result of his review of this literature and whether these conclusions properly support the Vitamin A and D regulations. This is particularly significant in the instant case since no findings have been made or even attempted with respect to ascertaining the purported levels of toxicity for Vitamins A and D.

7. Plaintiffs respectfully submit that the discovery sought by their notice of deposition is necessary and proper for a determination of whether the Commissioner acted reasonably in promulgating the Vitamin A and D regulations. If, for example, the defendants cannot furnish a proper basis for arriving at the levels specified in the regulations, surely the regulations would have to be considered arbitrary. If, on the other hand, a proper

formulation of these levels was made, there can be no legitimate reason for attempting to prevent disclosure of the scientific basis for the defendants' decision on these regulations.

8. The omissions and inadequacies in the record referred to above, frustrate the proper scope of review by this Court even under the limited theory proposed by defendants. It is, therefore, respectfully submitted that full access to discovery procedures is necessary herein in order to enable this Court to review the action of the defendant upon all of the factors and information which were before the administrative agency. Consequently, defendants' motion to vacate the notice of deposition should be denied.

MILTON A. BASS

Sworn to before me this
26th day of December, 1973.

JACOB LAUFER
NOTARY PUBLIC, State of New York
No. 31-4502286
Qualified in New York County
Commission Expires March

NLR:lw
73-2562

AFFIDAVIT OF NAOMI L. REICE WITH AFFIDAVIT OF STEPHEN MC NAMARA ANNEXED
(Filed December 13, 1973)

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,

Plaintiffs,

-against-

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

73 Civ. 3648 MEF

STATE OF NEW YORK)
COUNTY OF NEW YORK : ss.:
SOUTHERN DISTRICT OF NEW YORK)

NAOMI L. REICE, being duly sworn, deposes and says:

I am an Assistant United States Attorney in the office of Paul J. Curran, United States Attorney for the Southern District of New York, attorney for the defendants herein. This affidavit accompanies the affidavit of Stephen H. McNamara and the exhibits therewith. The exhibits to the affidavit of Mr. McNamara, which are copies of the medical articles referred to in the bibliography included in the record already on file with the Court, are provided for the convenience of the Court if the Court deems necessary further material when ruling upon the outstanding motions before it and any additional matters that may arise.

S/
NAOMI L. REICE
Assistant United States Attorney

Sworn to before me this
14th day of December, 1973.

S/

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,

Plaintiffs,

against

CASPAR W. WEINBERGER, Secretary of Health, Education, and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

73 Civ. 3448

AFFIDAVIT

County of Montgomery)
State of Maryland) ss

Stephen H. McNamara, being first duly sworn, deposes and says:

I am an attorney employed by the United States Department of Health, Education, and Welfare, Office of the General Counsel, Food and Drug Division, which provides legal services to the United States Food and Drug Administration.

When the Commissioner of Food and Drugs promulgated the Notice of Proposed Rulemaking concerning prescription status for high dosages of vitamins A and D in the Federal Register of December 14, 1972 (37 F.R. 26618), a listing of a number of pertinent articles regarding these vitamins was placed on file with the Hearing Clerk for public view and use in commenting on the proposal. (The public availability of this listing was announced in the Notice of Proposed Rulemaking. A copy of the listing should appear in volume one of the copy of the record which is already on file with the Court.)

Many of the comments, including the comment filed by plaintiff National Nutritional Foods Association, discussed the contents of these articles.

The articles themselves were not placed on display since they had been published in various medical journals and the citations are sufficient for securing copies of the articles in medical libraries. (Such citation is the medical analog of the legal custom of citing

published judicial decisions, legal articles, etc., in briefs, etc. without attaching copies.) Pursuant to my request, the Bureau of Drugs Library has assembled copies of the articles, which accompany this Affidavit, for the Court's reference in this case.

Stephen H. McNamara

Stephen H. McNamara

Subscribed and sworn to before me this 9th day of November, 1973, in the County and State aforesaid.

Francis E. McKay

Notary Public

MY COMMISSION EXPIRES
JULY 1, 1974

OPINION OF DISTRICT COURT VACATING NOTICE OF DEPOSITION AND DISMISSING COMPLAINT

UNITED STATES DISTRICT COURT (Filed April 5, 1974)
SOUTHERN DISTRICT OF NEW YORK

- x

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION AND SOLGAR CO., INC.,

Plaintiffs,

-against-

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

73 Civ. 3448

OPINION

- x

A P P E A R A N C E S :

Bass & Ullman, Esqs.
New York, N.Y.
Attorneys for Plaintiffs
Milton Bass, Esq.,
Of Counsel

Paul J. Curran, United States Attorney
for the Southern District of New York
New York, N.Y.
Attorney for Defendants
Naomi L. Reice, Assistant United States Attorney
Of Counsel

FRANKEL, D.J.

On October 1, 1973, regulations of the Food and Drug Administration became effective requiring that preparations of Vitamin A and Vitamin D in excess of 10,000 IU

(international units) per dosage unit and 400 IU per dosage unit, respectively, be restricted to prescription sale and that such vitamins be labeled accordingly. 21 C.F.R. §§3.94 and 3.95 (1973). The regulations were declared to have been promulgated to implement the "efficient enforcement" of §§502(a), (f), and (j) and 503(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§352(a), (f), and (j) and 353(b), under the general authority of the Act's §701(a), 21 U.S.C. §371(a), and pursuant to powers delegated to the Commissioner by 21 C.F.R. §2.120(a)(1)(1973).

Plaintiffs, involved in the manufacture, distribution, and sale of Vitamins A and D, filed suit on August 6, 1973, seeking declaratory and injunctive relief against the regulations. Their motion for a preliminary injunction was denied on September 25, 1973. National Nutritional Foods Ass'n v. Weinberger, 366 F.Supp. 1341, aff'd Docket No. 73-2430 (2d Cir., December 11, 1973).

Defendants have now moved for summary judgment dismissing the complaint. Counsel have made extensive submissions, and the court has heard further oral argument, supplementing the things read and heard on the motion for a

preliminary injunction. For reasons hereinafter outlined, the complaint is now to be dismissed.

I.

Plaintiffs claim that the questioned regulations were issued by the Commissioner without statutory authority. They argue that the legislative history of the prescription drug statute, 21 U.S.C. §353(b)(1)[1] reveals a purpose to prohibit regulations of this kind. The history shows, plaintiffs say, that the prescription requirement was meant to be for case-by-case determination in court, not for administrative rules like those before us. This intended limitation, they argue, may not be surmounted or avoided by the more general authority of the Commissioner to issue regulations under 21 U.S.C. §371(a). These contentions have substance. Having considered them, however, the court concludes that the legislative history is by no means clear enough to preclude a look at the statutory text,[2] and that the legislative mandate as a whole sustains the agency's position.

The Food, Drug and Cosmetic Act (the Copeland Act), 21 U.S.C. §301 et seq., was passed in 1938, superseding a 1906 statute touching the subject (the Wiley Act, c. 3915, 34 Stat. 768). The new Act was designed to respond to "profound changes in methods of manufacturing and selling foods and drugs" which had developed since 1906 and to remedy "textual weaknesses in the measure that were not foreseen when it was enacted." 79 Cong. Rec. 4758 (remarks of Sen. Copeland); see generally Jackson, Food and Drug Legislation in the New Deal (1970). Section 503(b) of the Act, 21 U.S.C. §353(b) (the prescription drug statute), was further amended in 1951 by the Durham-Humphrey Amendment, c. 578, 65 Stat. 648 (1951). This amendment and its history are the central subjects of plaintiffs' case.

The general purpose of the 1951 legislation was to adapt the Food, Drug and Cosmetic Act—

> "to deal realistically with the labelling and dispensing of drugs that may be sold only upon the prescription of licensed practitioners. Its provisions are remedial in the sense that they are intended to protect the public from abuses in the sale of potent prescription medicines. They will also relieve retail pharmacists of unnecessary restrictions in the dispensing of drugs that are safe for use without medical

supervision." S. Rep. No. 946, 82d Cong., 1st Sess. cited in 1951 U.S.Code Cong. and Admin. News 2454.

Accordingly, the amended section 503 created a new prescription requirement encompassing a statutory definition of drugs that may be dispensed only on prescription and specifying the conditions under which these drugs may be dispensed. Before, the law had simply commanded that the labeling of drugs bear adequate directions for use. While the Commission had provided some regulatory suasion,[3] it had been for the drug manufacturer to make the primary determination as to whether a prescription was necessary; the resulting lack of uniformity had left the retail druggist adrift in identifying his statutory (and health) obligations. One manufacturer might determine that a prescription legend was required for the same drug that a competing manufacturer considered suitable for over-the-counter sale. See H.R. Rep. No. 700, 82d Cong., 1st. Sess.3 (1951). As originally proposed, in H.R. 3298, the amended §503(b) would have conferred authority on the F.D.A. to issue an administrative list of drugs requiring prescription

prior to sale. While this provision was opposed by many drug manufacturers, it remained in the bill as reported out by the House Committee on Interstate and Foreign Commerce. Among the considerations which influenced the Committee in its decision to retain this aspect of the bill was the recognition that "the task of determining which drugs shall be sold only on prescription is, in its nature, essentially a legislative or rule-making function, unsuited for solution solely through the judicial process." H.R. Rep. No. 700, supra at 10.

A minority report asserted that "the present method which leaves this determination [of whether a prescription is required] to the courts, should be left unchanged except that a proper standard to be applied in determining whether a drug is dangerous should be incorporated in the statute." Id. at 28. The minority argued that providing the Administrator with power to issue regulations was a "dangerous delegation of authority" which would "add to present difficulties by increased bureaucratic regulation." Id.

H.R. 3298 reached the floor of the House on July 31, 1951, 97 Cong. Rec. 9235 (1951). The minority

view on handling the prescription requirement gathered support, on stated grounds both of general principle and of specific hostility to the then Administrator. On August 1, Congressman O'Hara of Minnesota introduced an amendment to strike the sections of the bill providing for the promulgation of an administrative list of drugs requiring a prescription for sale. The amendment carried. In its amended form H.R. 3298 was passed by the House and sent to the Senate, where it was reported out favorably and passed with minor amendments (and no significant debate) on October 15, 1951.

The Senate Committee which considered H.R. 3298 as passed by the House had before it both H.R. 3298 and a companion Senate bill, S. 1186 with various amendments in the nature of a substitute by Senator Humphrey designed to reintroduce the administrative list. While the Committee ultimately accepted the House version, it noted that the statutory definition simpliciter would be difficult or impossible to administer. The Committee Report explicitly contemplated the formulation of implementing regulations under 21 U.S.C. §371(a) to effectuate the statutory objective of protecting the public

health:

"In order to give this general definition a more precise meaning so that it may be applied with greater uniformity by the drug trade the Administrator can exercise the authority he has under section 701(a) of the Federal Food, Drug, and Cosmetic Act to issue interpretative regulations. It is to be understood that the inclusion of the statutory definition does not, of course, in any way derogate from the Administrator's authority to interpret and enforce the definition through the issuance of any regulations necessary or appropriate to protect the public from indiscriminate dispensing of drugs over the counter when they may be unsafe for use without the supervision of a practitioner licensed by law to administer such drugs.

"As previously stated, the committee considered S. 1186 together with H.R. 3298. S. 1186 would have authorized the Federal Security Administrator to list by name or class the drugs which he considered within the statutory definition. The grant of such administrative authority was objected to as an unnecessary regulation of the drug industry, and the committee concluded that administrative listing is not necessary at this time. It was felt that the statutory definition, together with the authority to make interpretative regulations, could bring an end to the existing confusion in drug labeling and that uniformity can be achieved through cooperative efforts of the drug industry and the Food and Drug Administration working under the statutory plan. If the present confusion is not ended by this legislation it will then be time enough to consider the need for the administrative listing approach.

* * *

> "Furthermore, in determining whether a drug is safe for use without medical supervision, there must be taken into consideration not only the drug's toxicity, but also other potentialities for harmful effect, the method by which it is used and the collateral measures necessary to its safe use. The broad language of the definition contained in this subparagraph is intended to comprehend all drugs that in fact should be administered under medical supervision in order to insure their safe use. Such difficult borderline cases as may arise under this definition can be dealt with under the interpretative and rule-making power provided for in section 701(a) of the act." S. Rep. No. 946, 82d Cong., 1st Sess., cited in 1951 U.S. Code Cong. and Admin. News 2457, 2462 (emphasis added).

In these expressions at least, there was a plain understanding that whatever specific rule-making powers were given to the F.D.A., the Commissioner would be required and expected to use his §701(a) power "to promulgate regulations for the efficient enforcement of this Act" in making the prescription requirement effective. As for the House, if it rejected the broad project of an "administrative list," it left §701(a) intact and nowhere indicated a purpose to render that section inoperative for purposes of the new prescription provision.[4]

Wherever the legislative history alone might leave us, the Commissioner's position finds solid support in §701(a) of the Act, 21 U.S.C. §371(a), and judicial as well as administrative constructions of this provision. Section 701(a) empowers the Commissioner, as delegee of the Secretary of Health, Education and Welfare, 21 C.F.R. §2.120 (1973), "to promulgate regulations for the efficient enforcement of" the Act, including the Act's prescription requirement in §353(b). Plaintiffs argue this is authority for mere "housekeeping" provisions, and they contrast subsection (e)[5] with subsection(a) of §701 to buttress the argument.[6] But the contention is not only at war with a considerable body of administrative practice;[7] it is also contrary to controlling judicial authority. Weinberger v. Hynson, Westcott & Dunning, 412 U.S. 609 (1973), sustained the F.D.A's authority under §701(a) to create an "administrative summary judgment procedure" (p. 617) having the drastic consequence, in cases to which it applied, of withdrawing approval of new drug applications without an evidentiary hearing. The administrative action was upheld as a valid instance of "particularizing standards through the

rulemaking process,"[8] deemed necessary and proper to prevent the "paralysis" of the administrative process which "would result if case-by-case battles in the courts were the only way to protect the public against unsafe or ineffective drugs." P. 626. Equally enlightening, if not technically "square" authority, is the pronouncement in Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645, 653 (1973), that the agency's power to determine "new drug" status in its own administrative proceedings was "implicit in the regulatory scheme" though "not spelled out in haec verba . . . ." Again, the construction was powerfully influenced by the recognition that a different view "would seriously impair FDA's ability to discharge the responsibilities placed on it by Congress." CIBA Corp. v. Weinberger, 412 U.S. 640, 643 (1973).

Our Court of Appeals has recognized similarly that "the Commissioner has the power to issue binding interpretative regulations," citing to another example of the authority sustained under §701(a), Abbott Laboratories v. Gardner, 387 U.S. 136 (1967), and observing that "the particularization of a statute by rule-making is not only acceptable in lieu of protracted piecemeal

litigation . . . but is the preferred procedure. . . ." CIBA-Geigy Corporation v. Richardson, 446 F.2d 446, 468 (1971). This principle, applied in the instant case, implements our duty to treat the statute, with its paramount concern for life and health, "as a working instrument of government and not merely as a collection of English words." United States v. Dotterweich, 320 U.S. 277, 280 (1943); see also United States v. Bacto-Unidisk, 394 U.S. 784, 798 (1969); United States v. Sullivan, 332 U.S. 689, 696 (1948); Permian Basin Area Rate Cases, 390 U.S. 747, 776 (1968). The recent approval of legislative rulemaking power under a section of the Truth In Lending Act very like §701(a) in language, Mourning v. Family Publications Service, Inc., 411 U.S. 356, 369 (1973), adds further support to the Commissioner's position here, as does the D.C. Circuit's determination that the Federal Trade Commission possesses substantive rulemaking power although the statute does not explicitly say so. National Petroleum Refiners Association v. F.T.C., 482 F.2d 672, 676-677, 689-91 (D.C. Cir. 1973), pet. for cert. filed, 42 U.S.L.W. 3376 (U.S. Nov. 20, 1973) (No. 806).

If the foregoing citations do not dictate mechanically the result herein, they point the clear path to decision. The "case-by-case battles in the courts" deemed compulsory by plaintiffs would have to be borne if the law required them. The result would be, of course, a rickety apparatus of non-regulation, with judges making disparate and uninformed decisions about when prescriptions should or should not be required. Such de novo courthearings could in no way inure "to [those] interests of the public that Congress was anxious to protect," Weinberger v. Bentex Pharmaceuticals, et al., 412 U.S. 645, 653 (1973). It seems fortunate that the Act, read sensibly and as a whole, requires no such unhappy interpretation.

II.

Plaintiffs contend that they should have a de novo "trial," preceded by considerable discovery, to test the questioned regulations. There is no warrant for such explorations or for an evidentiary hearing of any kind. The agency was not required to hold a trial-type hearing before issuing its regulations, and none is either required or permitted in the court. It is sufficient

that the public, including the plaintiffs, were "given a significant opportunity prior to promulgation of . . . [the] . . . rule[s] to ventilate the policy and empirical issues at stake through written submissions." National Petroleum Refiners Association v. Federal Trade Comm., 482 F.2d 672, 693 (D.C. Cir. 1973), pet. for cert. filed, 42 U.S.L.W. 3376 (U.S. Nov. 20, 1973) (No. 806). Unlike the rare cases in which the absence of an administrative record may require the taking of evidence in court, e.g., Citizens to Preserve Overton Park v. Volpe, 401 U.S. 402, 419-420 (1971), there is a voluminous and unstinting record here. Some 46 volumes in size, "it consists of the submissions made in response to the invitations issued for written comments." Automotive Parts & Accessories v. Boyd, 407 F.2d 330, 331 (D.C. Cir. 1968). Plaintiffs had full opportunity to present everything they thought germane. The agency, referring to the extensive materials it received, has sufficiently "articulate[d] its bases and purposes" in promulgating the regulations. Buckeye Power v. EPA, 481 F.2d 162, 170-71 (6th Cir. 1973);

see also Associated Indus. of N.Y.S. Inc. v. Dept. of L., 487 F.2d 342, 354 (2d Cir. 1973); Mobil Oil Corporation v. Federal Power Commission, 469 F. 2d 130, 140 (D.C. Cir. 1972), cert. den., 412 U.S. 931 (1973); International Engineering Company v. Richardson, 361 F.Supp. 818, 823-25 (D.D.C. 1973).

In rulemaking of this sort, where the regulations must stand unless they are deemed irrational or arbitrary and capricious, Associated Indus. of N.Y.S. Inc. v. Dept. of L., 487 F.2d 342, 348 (2d Cir. 1973); Bunny Bear, Inc. v. Peterson, 473 F.2d 1002, 1005-06 (1st Cir. 1973); Unimed, Inc. v. Richardson, 458 F.2d 787, 789 (D.C. Cir. 1972); Boating Industry Association v. Boyd, 409 F.2d 408, 411 (7th Cir. 1969); Citizens Band Association v. United States, 375 F.2d 43, 53-54 (9th Cir. 1967), it would be "sufficient that the regulations be supported by evidence in [the Commissioner's] files, or even by [his] experience." Consumers Union of United States, Inc. v. Consumer Product Safety Commission, No. 73-1617, slip op. at 1150 (2d Cir. Jan. 4, 1974). The case

against plaintiffs is far stronger; in this domain of medical judgment, where certainty is not attainable and special caution to safeguard health is compelled, the prudent and easily managed restrictions the Commissioner has required are solidly supported by the materials that were before him and have been lodged with the court.

In any case it is clear that the main, if not the exclusive, object plaintiffs pursue is an exploration of the mental processes by which the Commissioner reached his results. Such explorations are rarely to be countenanced. United States v. Morgan, 313 U.S. 409, 422 (1941); see also National Nutritional Foods Association v. Food and Drug Administration, No. 73-2129 (2d Cir. Feb. 1, 1974), especially when, as here, the Commissioner's rationale is sufficiently articulated to allow for meaningful judicial review. Citizens to Preserve Overton Park v. Volpe, 401 U.S. 402, 420 (1971). No showing has been made to justify the extraordinary inquiry plaintiffs propose.

It is abundantly clear, then, that the court should, and it does, vacate plaintiffs' notice to depose defendant Commissioner or his designees at an examination to which deponents would be required to bring "any and all books, correspondence, records, medical reports and literature relating to their determination of the dosage levels of Vitamins A and D which are in issue . . . ." In sum, there are no factual issues to be tried. The administrative record was properly made. It is in no pertinent sense incomplete. It leads, as has been stated, to a ruling that the regulations are by no means arbitrary, capricious, or otherwise infirm. In so holding, the court has reconsidered the propositions of law underlying the denial of a preliminary injunction. Those premises are now adhered to and reaffirmed.

Plaintiffs' notice of deposition is vacated. Defendants' motion for summary judgment is granted. The complaint is dismissed.

So ordered.

Dated: New York, New York
April 5, 1974

Marvin E. Frankel
U.S.D.J.

FOOTNOTES:

1.

"(b)(1) A drug intended for use by man which—

" (A) is a habit-forming drug to which section 352(d) of this title applies; or

"(B) because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug; or

"(C) is limited by an approved application under section 355 of this title to use under the professional supervision of a practitioner licensed by law to administer such drug,

shall be dispensed only (i) upon a written prescription of a practitioner licensed by law to administer such drug, or (ii) upon an oral prescription of such practitioner which is reduced promptly to writing and filed by the pharmacist, or (iii) by refilling any such written or oral prescription if such refilling is authorized by the prescriber either in the original prescription or by oral order which is reduced promptly to writing and filed by the pharmacist. The act of dispensing a drug contrary to the provisions of this paragraph shall be deemed to be an act which results in the drug being misbranded while held for sale."

2. See Greenwood v. United States, 350 U.S. 366,374 (1956) (Frankfurter, J.).

3. In 1944, the F.D.A. promulgated regulations designed to provide some guidance as to what drugs would be exempted from various warning requirements on their labels if only prescription sale was allowed. These standards were similar to those later incorporated in the Durham-Humphrey Amendment. See 21 C.F.R. §1.106 (b)(1) and (b)(2) (ii)(1949).

4. Contemporary trade circles recognized that this would be the case as well. See Dunn, The New Prescription Drug Law, 6 Food, Drug, Cosm. L.J. 951, 955-56 (1951).

5. §701(e), 21 U.S.C. §371(e) sets up structured procedures for promulgating regulations for specified purposes. Regulations issued under six specified statutes require that any proposed regulations be published by the Secretary. Within 30 days, if objection is received, a public hearing will be held "for the purpose of receiving evidence relevant and material to the issues raised by such objections." The resulting regulations must contain detailed findings of fact and be based on substantial evidence in the record of the hearing. The original Act required that a hearing be held and a public record established before any regulations could be issued or amended. Later amendments allowed regulations meeting no opposition to be promulgated by this expedited mechanism. C. 143, 68 Stat. 55 (1954); c.861, §2, 70 Stat. 919 (1956); see Forte, Fair Hearing in Administrative Rule Making: A Recent Experience Under the Federal Food, Drug and Cosmetic and Fair Packaging and Labeling Acts, 1968 Duke L.J. 1, 11-17

Six portions of the Act to which the §701(e) procedures apply are: §401, 21 U.S.C. §341 (establishing definitional identity and quality standards for certain foods); §403(j), 21 U.S.C. §343(j) (labeling requirements for special dietary foods); §404(a), 21 U.S.C. §344 (a) (emergency permit control system); §406(a), 21 U.S.C. §346 (establishment of tolerances for poisonous ingredients in food); §502(d), 21 U.S.C. §352(d)(designation of habit forming drug derivatives); §502(h), 21 U.S.C. §352(h) (packaging requirements for certain drugs).

6. Plaintiffs argue that §701(a) regulations are "interpretative" in the sense that they are promulgated without statutory authority and thus lack the force of law. This court accepts with alacrity the authoritative view that it is not profitable to explore the asserted distinction, Toilet Goods Association v. Gardner, 360 F.2d 677, 686 (2d Cir. 1966), aff'd, 387 U.S. 167 (1967), which is "fuzzy at best." Shapiro, The Choice of Rulemaking or Adjudication in the Development of Administrative Policy, 78 Harv. L. Rev. 921, 930, 959-60 (1965). However labeled, the questioned regulations merit the respect owed an expert agency. See Skidmore v. Swift & Company, 323 U.S. 134, 136-40 (1944). No label can justify the claims, hereinafter considered, that the court should hear and determine these problems of medical and pharmacological judgment de novo.

7. "The agency has promulgated a substantial number of rules under §701(a)." Hamilton, Rulemaking on a Record by the Food and Drug Administration, 50 Texas L. Rev. 1132, 1133 n. 10 (1972). Among such regulations of clearly substantive proportions are those governing food nutritional labeling, 21 C.F.R. §1.17 (1973), information panel labeling requirements, 21 C.F. R. §1.8(d)(1973), food fat labeling, 21 C.F.R. §1.18 (1973), specifications of the identity of products which may be sold under specific common or usual names, 21 C.F.R. §102.1-8 (1973), Good Manufacturing Practice Regulations, 21 C.F.R. §128 (1973), and the extensive series of review mechanisms encompassing the Over-The-Counter drug review program, 21 C.F.R. §130.301 (1973).

Wisconsin District Judge James E. Doyle has determined that the Good Manufacturing Practice Regulations specifying standards for "insanitary conditions," 21 C.F.R. 128(a)(A), promulgated under 701(a) are "not to be given automatic and decisive effect" in a criminal proceeding under 21 U.S.C. §331(a). United States v. Everett Fisheries, Inc., No. 72-Cr.-109 (W.D. Wisc. May 30, 1973). Unlike the instant case, Everett was a criminal prosecution. The statutory language allegedly violated through the violation

Footnote 7 cont'd

of the regulation was open to a variety of meanings and thus open to interpretation and argument. Cf. Pendergast and McMurray, The Constitutionality of the Good Manufacturing Practices Provision of the Federal Food, Drug & Cosmetic Act, 23 Bus. Lawyer 445, 449-55 (1968); Barnard, Good Manufacturing Practices Regulations in the Food Industry, 22 Food Drug Cosm. L.J. 511, 513-14 (1967). It is also noteworthy that Judge Doyle's decision antedated Weinberger v. Hynson, Westcott & Dunning, considered just below in the text.

8. The words were quoted, at p. 620, from FPC v. Texaco, 377 U.S. 33, 39 (1964), as stating a governing principle.

dosage forms were used almost exclusively for therapeutic purposes, case would be remanded for Overton type hearing in which court would scrutinize entire administrative record before Commissioner. 5 U.S.C.A. § 706(2)(A, E).

19. Drugs and Narcotics ⇐8

High dosage vitamins were not excludable fron statutory category of "prescription" drugs merely because they allegedly became unsafe only if used in violation of cautionary labeling or because some natural foods contain potent doses of certain vitamins. Federal Food, Drug, and Cosmetic Act, §§ 201(g), 503(b), (b)(1)(B), 21 U.S.C.A. §§ 321(g), 353(b), (b)(1)(B).

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Naomi Reice Buchwald, Asst. U. S. Atty. (Paul J. Curran, U. S. Atty., for the Southern District of New York, Gerald A. Rosenberg, Asst. U. S. Atty., New York City, of counsel), for defendants-appellees.

Kirkpatrick W. Dilling, and Dennis M. Gronek, Chicago, Ill. (Diana J.. Dilling, Chicago, Ill., of counsel), for amicus curiae National Health Federation.

Before LUMBARD, WATERMAN and MANSFIELD, Circuit Judges.

MANSFIELD, Circuit Judge:

This appeal by producers and vendors of vitamin preparations arises out of their unsuccessful attempt in the Southern District of New York to challenge regulations promulgated by the United States Food and Drug Administration ("FDA" herein) pursuant to § 701(a) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq. (the "Act" herein), which classify as "prescription drugs" all preparations of Vitamin A containing more than 10,000 IU (international units) per dosage form and of Vitamin D containing more than 400 IU per dosage form.[1] In the district court appellants sought declaratory and injunctive relief against the regulations, claiming that the FDA has no power to issue binding regulations under § 701(a), that the vitamin preparations at issue are foods and were improperly classified as prescription drugs under the Act, that plaintiffs were entitled to a *de novo* trial in the district court of factual issues going to the basis of the regulations and that the FDA's action in promulgating them was unsupported by substantial evidence. Appellants further contended that the "whole record" of the agency's action was not before the district court, and sought to depose the Commissioner of Food and Drugs ("Commissioner" herein). The district court, Marvin E. Frankel, Judge, vacated the notice of deposition and granted summary judgment dismissing the complaint.

Purporting to act under the general rule-making power vested in the Secretary of Health, Education and Welfare ("HEW" herein) by § 701(a) of the Act, 21 U.S.C. § 371(a), which authorizes him "to promulgate regulations for the efficient enforcement of this Act," the Commissioner, to whom this rule-making authority is delegated, 21 C.F.R. 2.120(a)(1), followed the notice-and-comment procedure outlined by § 4(c) of the Administrative Procedure Act,[2] 5 U.S.C. § 553(c), in promulgating the challenged regulations. First he published a statement in the Federal Register, 37 Fed.Reg. 26618, on December 14, 1972, giving notice of his proposal to adopt regulations which would require that, pursuant to the "prescription drug" law, § 503(b)(1) of the Act, 21 U.S.C. § 353(b),[3] Vitamins A and

1. Prior to plaintiffs' suit in the district court a petition for review of the FDA promulgation was dismissed by us for lack of jurisdiction. See Citizens for Truth in Nutrition v. FDA, Dkt. No. 73-2826 (2d Cir. Mar. 4, 1974).

2. See p. 1612, *infra*.

3. "(b)(1) A drug intended for use by man which—

"(A) is a habit forming drug to which section 352(d) of this title applies; or

"(B) because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures neces-

D in dosage units in excess of 10,000 IU and 400 IU, respectively ("higher dosage forms" herein) be restricted to prescription sale and deemed misbranded unless the label of the container in which they were sold or dispensed bore appropriate disclosure and warnings.

The Commissioner's initial statement advised that, according to medical literature, the ingestion of large dosages of Vitamins A and D over long periods could have serious toxic effects and that these vitamins were available over the counter in dosage forms many times the daily allowance recommended and published by the Food and Nutrition Board of the National Academy of Sciences—National Research Council ("NAS/NRC" herein). According to the Commissioner's statement the excess dosage forms were the subject of widespread promotion to the public for prophylaxis and treatment of a variety of diseases and disorders. The American Academy of Pediatrics had published a statement warning physicians regarding the various forms of toxicity that could result from intake of the large amounts of Vitamin A being recommended by vendors to the public in the press, on radio and on TV. Many types of serious adverse effects from ingestion of excessive amounts of Vitamins A and D were listed, including some that resulted in death. The recommended daily allowance ("RDA" herein) published by the Food and Nutrition Board of the NAS/NRC as between 4,500 and 5,000 IU of Vitamin A for older children and adults, 6,000 IU during pregnancy and 8,000 IU during lactation. For Vitamin D preparations the RDA was 400 IU for all age groups. The Commissioner placed on public view an extensive bibliography of the medical literature employed by the FDA in formulating its proposed regulations. The Commissioner's statement invited interested persons to file with the HEW within 60 days any written comments they might desire to submit with respect to the proposals, together with memoranda and briefs, all of which would be available for public inspection.

Over, 2,500 written comments were submitted by a wide cross-section of the public, including consumers, physicians, nurses, pharmacists, pharmaceutical manufacturers, health food store operators. Various organized consumer and other groups, including the Academy of Pediatrics, American Medical Association, and the Pharmaceutical Manufacturers Association also responded. Both plaintiffs in this case submitted extensive comments opposing the regulations. According to the Commissioner, the comments fell into three general categories: (1) Those who viewed the proposed regulations as suitable. This group included the American Medical Association, the American Academy of Pediatrics, various consumer groups, physicians and others; (2) Those who agreed that vitamins could be toxic, but at higher levels than those proposed by the Commissioner. In this group were the majority of the drug manufacturers and trade associations plus some consumers; and (3) Those who disagreed with the proposals entirely, taking the view that such vitamin preparations are food and that consumption of desired quantities is an individual right. These comments came mostly from consumers and health food establishments.

In a report published in the Federal Register on August 2, 1973, 38 Fed.Reg.

> sary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug; or
>
> "(C) is limited by an approved application under section 355 of this title to use under the professional supervision of a practitioner licensed by law to administer such drug,
>
> shall be dispensed only (i) upon a written prescription of a practitioner licensed by law to administer such drug, or (ii) upon an oral prescription of such practitioner which is reduced promptly to writing and filed by the pharmacist, or (iii) by refilling any such written or oral prescription if such refilling is authorized by the prescriber either in the original prescription or by oral order which is reduced promptly to writing and filed by the pharmacist. The act of dispensing a drug contrary to the provisions of this paragraph shall be deemed to be an act which results in the drug being misbranded while held for sale."

tions went into effect. In a further opinion dated April 5, 1974, published at 376 F.Supp. 142 (S.D.N.Y.1974), Judge Frankel granted defendant's motion for summary judgment dismissing the complaint and upheld the regulations as having been promulgated pursuant to the Commissioner's authority under the Act. He further held that plaintiffs were not entitled to a *de novo* trial, preceded by discovery, to test the regulations, since the rule-making procedure followed by the FDA, which resulted in voluminous comments, was adequate and the regulations were not irrational, arbitrary or capricious, which he deemed to be the standard of review. From this decision plaintiffs appeal.

Discussion

Appellants have launched a multifaceted attack upon the challenged regulations and the district court's grant of summary judgment. They contend that the FDA has no authority to issue regulations having the binding effect of law, other than those regulations which must be issued under the adjudicatory hearing procedures provided by § 701(e) of the Act, 21 U.S.C. § 371(e).[5] They argue that regulations issued under § 701(a), which does not provide for a hearing, at best represent merely administrative interpretations of the substantive statutory law, enforceable only on a case-by-case basis that would insure *de novo* adjudication of all issues by the district court. They further assert that, even assuming *arguendo* that the FDA had the power to promulgate binding regulations, the present ones are deficient because they are unsupported by substantial evidence and the record fails to contain adequate findings and a sufficient explanation of the basis and rationale of the FDA's action to enable a reviewing court to determine whether the FDA acted within the scope of its statutory authority and on the basis of supporting

5. "(e)(1) Any action for the issuance, amendment, or repeal of any regulation under section 341, 343(j), 344(a), 346, 351(b), or 352(d) or (h), of this title shall be begun by a proposal made (A) by the Secretary on his own initiative, or (B) by petition of any interested person, showing reasonable grounds therefor, filed with the Secretary. The Secretary shall publish such proposal and shall afford all interested persons an opportunity to present their views thereon, orally or in writing. As soon as practicable thereafter, the Secretary shall by order act upon such proposal and shall make such order public. Except as provided in paragraph (2) of this subsection, the order shall become effective at such time as may be specified therein, but not prior to the day following the last day on which objections may be filed under such paragraph.

"(2) On or before the thirtieth day after the date on which an order entered under paragraph (1) of this subsection is made public, any person who will be adversely affected by such order if placed in effect may file objections thereto with the Secretary, specifying with particularity the provisions of the order deemed objectionable, stating the grounds therefor, and requesting a public hearing upon such objections. Until final action upon such objections is taken by the Secretary under paragraph (3) of this subsection, the filing of such objections shall operate to stay the effectiveness of those provisions of the order to which the objections are made. As soon as practicable after the time for filing objections has expired the Secretary shall publish a notice in the Federal Register specifying those parts of the order which have been stayed by the filing of objections and, if no objections have been filed, stating that fact.

"(3) As soon as practicable after such request for a public hearing, the Secretary, after due notice, shall hold such a public hearing for the purpose of receiving evidence relevant and material to the issues raised by such objections. At the hearing, any interested person may be heard in person or by representative. As soon as practicable after completion of the hearing, the Secretary shall by order act upon such objections and make such order public. Such order shall be based only on substantial evidence of record at such hearing and shall set forth, as part of the order, detailed findings of fact on which the order is based. The Secretary shall specify in the order the date on which it shall take effect, except that it shall not be made to take effect prior to the ninetieth day after its publication unless the Secretary finds that emergency conditions exist necessitating an earlier effective date, in which event the Secretary shall specify in the order his findings as to such conditions."

evidence. They argue that the district court improperly used the "arbitrary, capricious" rather than the "substantial evidence" standard of review but that even the former could not be met here, in view of the inadequacy of the record, which fails adequately to demonstrate the basis of the Commissioner's action.

If this case had been one governed by hearing requirements like those in § 701(e) or if the district court had held a *de novo trial*, appellants argue, crucial factual issues would have been resolved in their favor. They allege that they would have demonstrated that Vitamins A and D at the dosage levels specified in the regulations are not "drugs" as that term is defined in § 201(g) of the Act, 21 U.S.C. § 321(g),[6] because they were not intended for use in the treatment or prevention of disease but as dietary supplements, and that they could not lawfully be classified as "prescription drugs" under § 503(b)(1)(B) of the Act, 21 U.S.C. § 353(b)(1)(B), since the products are not toxic at the levels established by the regulations and are not inherently unsafe when used without prescription in a rational manner, but can become unsafe only when misused or used irrationally. The effect of the action of the FDA and of the district court, say appellants, is to withdraw a food from the market without a hearing and without findings, contrary to Congress' intent in enacting the prescription drug statute.

The FDA's Rule-Making Authority

Resolution of the issues raised by appellants requires an analysis of the FDA's rule-making power and of the federal court's role in reviewing the exercise of that power. As enacted in 1938 § 701 of the Food and Drug Act, 21 U.S.C. § 371, contained two grants of authority to the FDA to promulgate regulations. Section 701(a) broadly grants:

> "(a) The authority to promulgate regulations for the efficient enforcement of this chapter, except as otherwise provided in this section, is vested in the Secretary."

No conditions were expressly imposed upon this expansive grant of authority. A few paragraphs thereafter, on the other hand, Congress prescribed in §§ 701(e) and (f) an elaborate procedure that must be followed by the FDA in promulgating regulations with respect to certain specifically enumerated subjects (e. g., standards of identity, 21 U.S.C. § 341, branding of food for special dietary uses, 21 U.S.C. § 343(j), distribution of potentially contaminated foods, 21 U.S.C. § 344(a)), including notice, comments by interested parties, promulgation of proposed rules, filing of objections, a public evidentiary hearing if requested by a "party adversely affected," and a court of appeals review, 21 U.S.C. § 371(e), (f).

Congress did not expressly spell out the authoritative effect that should be given to regulations promulgated under §§ 701(a) and 701(e).[7] This naturally leads one to wonder, in view of the care with which Congress spelled out the elaborate § 701(e) procedure, whether it intended any limits on the apparently expansive delegation of rule-making power granted by § 701(a), and specifically whether (as appellants urge) the latter was meant merely to grant authority to issue interpretive, non-binding advisory opinions with respect to matters

6. "(g)(1) The term 'drug' means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement of any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clauses (A), (B), or (C) of this paragraph; but does not include devices or their components, parts, or accessories."

7. The legislative history does confirm that § 701(e) regulations "are not merely interpretive. They have the force of law and must be observed." H.Rep.No.2139, 75th Cong., 3d Sess. (1938), p. 12. However, there is no statement indicating that § 701(a) regulations were to have similar effect.

of lesser importance than those promulgated here, which serve the rather important function of defining the status of a product as a food or drug and restricting certain products to prescription sale as drugs.

[1] The FDA, like most federal agencies, does have power to issue "interpretive" regulations. Agency interpretations of substantive statutory law have been viewed as "not controlling upon the courts by reason of their authority," Skidmore v. Swift & Co., 323 U.S. 134, 140, 65 S.Ct. 161, 164, 89 L.Ed. 124 (1944), but merely as "a body of experience and informed judgment to which courts and litigants may properly resort for guidance," *id.* Appellants urge upon us the view that all regulations issued pursuant to § 701(a) are advisory only, and are subject to *de novo* challenge in court enforcement proceedings. This position has frequently been taken by members of the drug industry:

> "Interpretive regulations . . . issued pursuant to section 701(a) consist of FDA opinions of the meanings of various sections of the Act, and opinions as to the impact of those sections on particular fact situations. They have advisory effect only. That is, they tell private parties what the FDA position will be in an enforcement proceeding. But in that proceeding, the court must consider, on a full evidentiary showing, whether the particular conduct challenged by the FDA pursuant to its announced enforcement policy is a violation of the Act." Munsey, Survey of Current Legal Problems in the Drug Area, 23 Food, Drug and Cosmetic L.J. 449, 454 (1968).

See also Cody, Authoritative Effect of FDA Regulations, 24 Food, Drug and Cosmetic L.J. 195, 196 (1969).

[2] A court may well consider it within its power to review the legality of some types of regulations which seek at length to flesh out the terms of a broad statute, especially when the regulations themselves are rather imprecise. In such cases a court in an enforcement proceeding will in any event be forced to develop a considerable factual record to determine whether there has been a violation of the regulation. But, as Judge Frankel observed, attempts to draw a hard and fast line between "interpretive" and "substantive" regulations have been rather unrewarding. The line of demarcation between the two is often far from clear. Faced with the argument advanced here by appellants we stated in Toilet Goods Ass'n v. Gardner, 360 F.2d 677, 686 (2d Cir. 1966), affd., 387 U.S. 167, 87 S.Ct. 1526, 18 L.Ed.2d 704 (1967), "Neither do we think anything is to be gained by an attempt at comprehensive review of the decisions; the many cases in this area are not truly reconcilable . . . ." We have come to recognize that, if the administrative process is to be practically effective, specific regulations promulgated pursuant to a general statutory delegation of authority must be treated as authoritative, whether labelled "substantive" or "interpretive," especially in areas where the agency possesses expertise not shared by the courts. In that event its views are unlikely to be disturbed by the court in an enforcement proceeding. See, e. g., Abbott Laboratories v. Gardner, 387 U.S. 136, 151–152, 87 S.Ct. 1507, 18 L.Ed.2d 681 (1967); CIBA–GEIGY Corp. v. Richardson, 446 F.2d 466, 468 (2d Cir. 1971). Where once we may have demanded proof of specific delegation of legislative authority to an agency purporting to promulgate substantive rules we have learned from experience to accept a general delegation as sufficient in certain areas of expertise.

[3] Whatever doubts might have been entertained regarding the FDA's power under § 701(a) to promulgate binding regulations were dispelled by the Supreme Court's recent decisions in Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 93 S.Ct. 2469, 37 L.Ed.2d 207 (1973), and its companion cases, Ciba Corp. v. Weinberger, 412 U.S. 640, 93 S.Ct. 2495, 37 L.Ed.2d 230 (1973); Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645, 93 S.Ct. 2488, 37

L.Ed.2d 235 (1973); USV Pharmaceutical Corp. v. Weinberger, 412 U.S. 655, 93 S.Ct. 2498, 37 L.Ed.2d 244 (1973). Those decisions interpreted § 701(a) as giving FDA the power to promulgate substantive regulations having the binding force of law rather than mere "interpretive" statements enforceable only on a case-by-case basis through plenary suits against those refusing to comply. The Court upheld the power of the FDA under § 701(a) to promulgate binding regulations which (1) defined the standards of evidence to be met by drug manufacturers called upon to demonstrate the efficacy of their products in new drug applications, and (2) permitted the dismissal without a hearing (i. e., by summary judgment) of an application failing to meet these standards. The Court further approved administrative determination by the FDA of whether a product was a "new drug" within the meaning of the Act. In sanctioning the equivalent of an administrative summary judgment procedure Justice Douglas, speaking for the Court, stated:

> "If FDA were required automatically to hold a hearing for each product whose efficacy was questioned by the NAS-NRC study, even though many hearings would be an exercise in futility, we have no doubt that it could not fulfill its statutory mandate to remove from the market all those drugs which do not meet the effectiveness requirements of the Act." 412 U.S. at 621, 93 S.Ct. at 2479.

The same pragmatic view was taken with respect to the FDA's power to determine administratively the "new drug" status of a product, the Court stating that the FDA could not "administer the Act intelligently and rationally unless it has authority to determine what drugs are 'new drugs'", 412 U.S. at 624, 93 S.Ct. at 2480, and continuing with the observation:

> "To require separate judicial proceedings to be brought against each [drug manufacturer], as if each were the owner of a Black Acre being condemned, would be to create delay where in the interest of public health there should be prompt action. A single administrative proceeding in which each manufacturer may be heard is constitutionally permissible measured by the requirements of procedural due process." 412 U.S. at 625, 93 S.Ct. at 2481.

In Ciba Corp. v. Weinberger, 412 U.S. 640, 93 S.Ct. 2495, 37 L.Ed.2d 230 (1973), the FDA's power to determine "new drug status" in definitive administrative proceedings, as distinguished from the power to seek such determinations in case-by-case enforcement proceedings, was established beyond any serious question. The Court held that a district court may properly defer to the FDA's primary jurisdiction, and observed that in providing the FDA with a "second line of defense"—injunction proceedings and seizure actions—"the Act does not create a dual system of control—one administrative, the other judicial," 412 U.S. at 644, 93 S.Ct. at 2498. Finally the Court in *Bentex Pharmaceuticals, supra*, recognized the FDA's power to promulgate binding regulations not only for pragmatic reasons but on the ground that the FDA, by reason of its expertise, was better equipped to make such determinations than a court which is "without chemical or medical background," 412 U.S. at 652–653, 93 S.Ct. 2488, 37 L.Ed.2d 235.

[4–6] These decisions clearly point to the conclusion that the FDA may promulgate regulations of the type challenged here. Congress' establishment of a specific (and elaborate) procedure in § 701(e) authorizing the FDA to promulgate regulations in certain fields was in addition to and not in derogation of the general rule-making power granted to the FDA by § 701(a). Under the latter section, furthermore, the FDA may follow streamlined procedures designed to avoid the endless delays that have tended to paralyze adjudicatory hearings and

render them ineffective as a means of utilizing agency expertise.[8]

Our attention has not been directed to anything in the legislative history of §§ 701(a) and (e) that militates against these conclusions. On the contrary, over the last decade rule-making has been increasingly substituted for adjudication as a regulatory technique, with the support and encouragement of courts, at least where the regulation involves specialized scientific knowledge. See NLRB v. Wyman-Gordon Co., 394 U.S. 759, 89 S.Ct. 1426, 22 L.Ed.2d 709 (1968); Mourning v. Family Publications Serv., Inc., 411 U.S. 356, 93 S.Ct. 1652, 36 L.Ed.2d 318 (1973); National Petroleum Refiners Assn. v. FTC, 157 U.S.App.D.C. 83, 482 F.2d 672 (1973), cert. denied, 415 U.S. 951, 94 S.Ct. 1475, 39 L.Ed.2d 567 (1974); Anaconda Co. v. Ruckelshaus, 482 F.2d 1301 (10th Cir. 1973); United States v. Florida East Coast Railway, 410 U.S. 224, 93 S.Ct. 810, 35 L.Ed.2d 223 (1973). Where the objective is essentially legislative, i. e., to establish rules or principles by which an entire industry may be governed, the case-by-case adversary proceeding, in which the agency confronts a single alleged offender selected for suit with respect to a specific factual situation, has frequently proved to be an unsuitable method of enforcing the law, since it often resolves narrow issues of importance only to the immediate adversaries rather than broad questions of interest to the industry or the public. The rule-making proceeding, on the other hand, provides the agency with an opportunity first to receive a wide spectrum of views proffered by all segments affected by the proposed rule (e. g., manufacturers, vendors, doctors, consumers) and then in a legislative fashion to consider and choose from several alternatives or options rather than limit its decisions to narrow issues controlling a particular case. Furthermore, once binding regulations are promulgated, the industry and public are put on notice and may be guided accordingly rather than speculate as to the outcome of a seizure or enforcement suit. See Shapiro, The Choice of Rulemaking or Adjudication in the Development of Administrative Policy, 78 Harv.L.Rev. 921 (1965).

Whether the FDA's Rule-Making Power under § 701(a) Extends to "Prescription Drugs" as Defined in § 503(b)(1) of the Act

Appellants contend that, regardless what the FDA's rule-making power under § 701(a) may be with respect to other matters, the legislative history of the "prescription drug" statute, § 503(b)(1) of the Act, 21 U.S.C. § 353(b)(1), demonstrates that Congress intended to deny the agency the power to make binding rules specifying those products that would require a prescription. Congress, they argue, intended that the FDA must seek resolution of that issue through case-by-case enforcement proceedings. We disagree.

[7, 8] The legislative history of the prescription drug statute, which was enacted by Congress in 1951 as the Durham-Humphrey Amendment to the Act, sheds no clear light on the question of what rule-making authority Congress assumed or intended that the FDA would have in deciding what drugs must be sold only on prescription. Differing ver-

8. The proceedings under § 701(e) at issue in NNFA v. FDA, for example, were begun in 1962, 504 F.2d at 768. The notorious proceeding which established standards of identity for peanut butter lasted more than 10 years. See Hamilton, Rulemaking on a Record by the Food and Drug Administration, 50 Texas L.Rev. 1132, 1142–45 (1972).

Appellants contend that the use of a notice and comment procedure in this case was wholly gratuitous, and that the FDA can use procedures under § 701(a) so "streamlined" that objectants have no procedural rights. This is clearly not the case. When adopting a rule that purports to have the force of law, the agency is bound by the procedural requirements of § 4 of the Administrative Procedure Act, 5 U.S.C. § 553. Whatever the term "interpretive" may mean in other contexts, it seems apparent that the exemption from § 4 requirements provided in 5 U.S.C. § 553(b)(3)(A) for "interpretive rules" refers only to rules not intended to have the force of law.

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sions of the amendment, as they appeared first in the House and later in the Senate, delegated varying degrees of power to the FDA and were the subject of differing interpretations by members of Congress. Delving into the House and Senate Committee Reports and statements by members of Congress on the floor, one can find expressions construing the agency's power as interpretive only, with the issue of whether any product was a prescription drug to be determined by the court in enforcement proceedings.[9] On the other hand, the Senate Report issued in support of the legislation as it was finally enacted, which should be deemed more authoritative than statements by individual Congressmen at earlier stages before amendments were made, see Zuber v. Allen, 396 U.S. 168, 186, 90 S.Ct. 314, 24 L.Ed.2d 345 (1969); United States v. O'Brien, 391 U.S. 367, 385, 88 S.Ct. 1673, 20 L.Ed.2d 672 (1968), indicates that Congress intended the FDA to exercise its rule-making powers under § 701(a) in order to "enforce" the statute.[10] Were we required to decide the question solely on the legislative history we would lean to the view that Congress expected the FDA, particularly in view of its expertise, to promulgate from time to time *binding* interpretations of the standards set forth in the prescription drug statute, subject to judicial review, rather than leave the decision to the courts, which lack the medical and scientific knowledge essential to such decisions. Whatever doubts we might have had on the question, however, have been resolved by the Supreme Court's interpretation of the FDA's rule-making power in *Hynson* and its companion cases. Surely an agency which possesses the power to determine administratively what products are "new drugs" has the authority to decide what products are "prescription drugs."

The Adequacy of the Procedures Followed by the FDA

[9] Since § 701(a) of the Act, pursuant to which the challenged regulations were adopted, does not require an evidentiary hearing, the FDA was autho-

9. The report of the House minority committee whose position generally prevailed in that chamber stated an objection to the prescription drug provisions since they

> "would make basic changes in the method of determining which drugs are dangerous and may be sold only on prescription, and which drugs are safe and may be sold over the counter. We think the present method, which leaves this determination to the courts, should be left unchanged except that a proper standard to be applied in determining whether a drug is dangerous should be incorporated in the statute." H.Rep.No.700, 82d Cong., 1st Sess. (1951), p. 28.

The minority further suggested that providing the Federal Security Administrator with administrative power to list "prescription" drugs was "a dangerous delegation of authority" which would "add to the present difficulties by increased bureaucratic regulation." *Id.*

10. "In order to give this general definition a more precise meaning so that it may be applied with greater uniformity by the drug trade the Administrator can exercise the authority he has under section 701(a) of the Federal Food, Drug, and Cosmetic Act to issue interpretative regulations. It is to be understood that the inclusion of the statutory definition does not, of course, in any way derogate from the Administrator's authority to interpret and enforce the definition through the issuance of any regulations necessary or appropriate to protect the public from indiscriminate dispensing of drugs over the counter when they may be unsafe for use without the supervision of a practitioner licensed by law to administer such drugs." S.Rep.No.946, 82d Cong., 1st Sess. (1951), pp. 4-5, U.S.Code Cong. & Admin.Serv. p. 2457.

"Furthermore, in determining whether a drug is safe for use without medical supervision, there must be taken into consideration not only the drug's toxicity, but also other potentialities for harmful effect, the method by which it is used, and the collateral measures necessary to its safe use. The broad language of the definition contained in this subparagraph is intended to comprehend all drugs that in fact should be administered under medical supervision in order to insure their safe use. Such difficult borderline cases as may arise under this definition can be dealt with under the interpretative and rule-making power provided for in section 701(a) of the act." Id. at 8-9, U.S.Code Cong. & Admin.Serv. pp. 2461-2462.

rized to use the "notice and comment" procedure prescribed by § 4 of the Administrative Procedure Act, 5 U.S.C. § 553(c), which provides:

> "(c) After notice required by this section, the agency shall give interested persons an opportunity to participate in the rule making through submission of written data, views, or arguments with or without opportunity for oral presentation. After consideration of the relevant matter presented, the agency shall incorporate in the rules adopted a concise general statement of their basis and purpose. When rules are required by statute to be made on the record after opportunity for an agency hearing, sections 556 and 557 of this title apply instead of this subsection."

This procedure has been generally recognized as adequate for the purpose of airing issues, evidence, and relevant factors to be considered by an agency in determining whether a rule is to be promulgated and, if so, its terms. See, e. g., National Petroleum Refiners Assn. v. FTC, 157 U.S.App.D.C. 83, 482 F.2d 672 (1973), cert. denied, 415 U.S. 951, 94 S.Ct. 1475, 39 L.Ed.2d 567 (1974).

Before adopting the regulations the FDA scrupulously followed the procedure prescribed by § 4. Appellants and all others concerned were given ample notice of the proposed action and an opportunity to submit documents, data and arguments. Many groups including appellants took advantage of this opportunity and submitted extensive and detailed comments containing medical and scientific data, analyses, criticism, suggested revisions and alternative proposals. These extensive submissions were collated by the FDA in some 46 folders. Appellants not only set forth their own views and data in detail but were permitted to examine the opposing comments and data submitted by others and to examine and criticize the medical literature relied upon by the FDA. It is undisputed that the FDA gave consideration to this mass of information in deciding whether to promulgate its proposed regulations. Since the decision did not turn on precise factual issues or on the credibility of witnesses but represented a judgment based upon consideration of relevant medical and scientific data, we doubt that a trial-type adversary hearing would have shed any further light on the question of whether restriction of the sale of higher dosage levels of Vitamins A and D to prescription sale would be in the public interest. The question was one to be resolved on the basis of a general appraisal of the risk of toxicity. It is conceded that even with the regulations in effect a purchaser of preparations containing less than the IU content required for prescription could suffer the effects of excessive ingestion by consuming a larger number of the less potent dosage forms. However, the Commissioner believed from experience that the regulations would lessen the risk of excessive intake that would be presented by the availability across the counter of higher potencies in single dosage units.

[10, 11] Appellants contend that the district court erred in applying the "arbitrary, capricious" rather than the "substantial evidence" standard prescribed by 5 U.S.C. § 706(2)(E). We disagree. Section 706(2)(E) is restricted to agency action in which an evidentiary hearing is required. Since no such hearing was required in the present case the appropriate standard for review of a regulation promulgated pursuant to the "notice and comment" procedure has been recognized to be that specified by 5 U.S.C. § 706(2)(A), which authorizes a reviewing court to hold unlawful and set aside agency action, findings and conclusions found to be "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." See National Nutritional Foods Assn. v. FDA, 504 F.2d 761, 773 n. 8 (2d Cir. 1974); Consumer Union of United States v. Consumer Product Safety Commission, 491 F.2d 810 (2d Cir. 1974). Although the Supreme Court in Citizens to Preserve Overton Park v. Volpe, 401 U.S. 402, 91 S.Ct. 814, 28 L.Ed.2d 136 (1971), referred to the

substantial evidence test in connection with rule-making proceedings under 5 U.S.C. § 553, it later made clear in *Hynson* that this standard applies only to proceedings which are the subject of hearing provisions provided by 5 U.S.C. §§ 556 and 557 or to review of the record of an agency hearing provided by statute and that it did not apply to regulations promulgated by the FDA pursuant to § 701(a) of the Food, Drug and Cosmetic Act. See Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. at 622 n. 19, 93 S.Ct. 2469, 37 L.Ed.2d 207. See also Camp v. Pitts, 411 U.S. 138, 140–141, 93 S.Ct. 1241, 36 L.Ed.2d 106 (1973) (per curiam).

[12–14] The requirement in 5 U.S.C. § 553(c) that an agency promulgating rules pursuant to the "notice and comment" procedure "incorporate in the rules a concise general statement of their basis and purpose" certainly does not require the agency to supply specific and detailed findings and conclusions of the kind customarily associated with formal proceedings, Consumer Union of United States v. Consumer Product Safety Commission, 491 F.2d at 812. But this provision does not lessen or excuse the agency's obligation to publish a statement of reasons that will be sufficiently detailed to permit judicial review, Automotive Parts & Accessories Assn. v. Boyd, 132 U.S.App.D.C. 200, 407 F.2d 330, 338 (1968), and even under the "arbitrary, capricious" standard agency action will not be upheld where inadequacy of explanation frustrates review. Camp v. Pitts, 411 U.S. 138, 93 S.Ct. 1241, 36 L.Ed.2d 106 (1973); Citizens to Preserve Overton Park v. Volpe, 401 U.S. 402, 91 S.Ct. 814, 28 L.Ed.2d 136 (1971). Indeed the very absence of a detailed record of the type that would be made if an evidentiary hearing were held makes it advisable for the agency, in lieu thereof, to provide a thorough and comprehensible statement of the reasons for its decision. Where the agency's "finding is not sustainable on the administrative record made, then the . . . decision must be vacated and the matter remanded to [the agency] for further consideration." Camp v. Pitts, 411 U.S. at 143, 93 S.Ct. at 1244; cf. Kennecott Copper Corp. v. Environmental Protection Agency, 149 U.S.App.D.C. 231, 462 F.2d 846, 850 (1972) (remanding to the agency for explanation of the basis of its finding).[11]

[15] A failure of the agency adequately to explain its actions is not a warrant to the district court to conduct a *de novo* evidentiary hearing, Camp v. Pitts, *supra*. "[T]he focal point for judicial review should be the administrative record already in existence, not some new record made initially in the reviewing court." 411 U.S. at 142, 93 S.Ct. at 1244. Instead, the remedy under these circumstances is "to obtain from the agency, either through affidavits or testimony, such additional explanation of the reasons for the agency decision as may prove necessary." *Id.* at 143, 93 S.Ct. at 1244; cf. Kennecott Copper Corp. v. EPA, *supra*.

[16] Applying the foregoing principles here, a serious question is raised as to whether the Commissioner, in concluding that the higher level dosage forms of Vitamins A and D are "drugs," acted "in accordance with law," as that phrase is used in 5 U.S.C. § 706(2)(A). The question is posed by § 201(g) of the Act, 21 U.S.C. § 321(g), which defines a "drug" as an article recognized in the United States Pharmacopoeia or "intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease." Protection of the public health dictates that these definitions be construed liberally and that the FDA's determination be given considerable weight, United States v. An Article of Drug—Bacto-Un-

11. Although we have stated that regulations may be supported not only by the record but by the FDA's "experience," see Consumers Union of United States v. Consumer Product Safety Commission, 491 F.2d 810 (2d Cir. 1974), the agency's experience, to the extent that it provides a *factual* basis for a regulation under attack, must be a matter of record in order to qualify for consideration by a reviewing court.

idisk, 394 U.S. 784, 792, 798, 89 S.Ct. 1410, 22 L.Ed.2d 726 (1968), provided it is not unreasonable, Udall v. Tallman, 380 U.S. 1, 16–18, 85 S.Ct. 792, 13 L.Ed.2d 616 (1965), and has some support in the record, Camp v. Pitts, *supra*, 411 U.S. at 143, 93 S.Ct. 1241, 36 L.Ed.2d 106. Judge Frankel dismissed quickly the argument that Vitamins A and D were improperly classified as drugs, stating simply that "the products here are squarely within the literal language and evident meaning of the statute." However, since the district court's determination this court decided National Nutrition Foods Assn. v. FDA, 504 F.2d 761 (2d Cir. 1974) ("NNFA v. FDA" herein), which suggests that a greater inquiry by the district court is required. In that case, upon a petition to review FDA regulations fixing standards of identity and label statements for vitamin supplements sold as foods, which had been promulgated after an evidentiary hearing under § 701(e)(3) of the Act, 21 U.S.C. § 371(e)(3), we invalidated § 125.1(h),[12] which provided that any product containing more than the upper limit of the U.S. RDA per serving or daily recommended quantity (apparently 8,000 IU of Vitamin A and 400 IU of Vitamin D) is a drug. Judge Friendly reasoned that, although vitamins may be listed in the U.S. Pharmacopoeia or official National Formulary, this fact was not relied upon by the parties or the FDA as the reason for classifying these potencies as drugs and it represented at best a *post hoc* rationalization which would not suffice to validate the regulation, see Burlington Truck Lines, Inc. v. United States, 371 U.S. 156, 168, 83 S.Ct. 239, 9 L.Ed.2d 907 (1962). He further concluded that the argument would in any event prove too much, since it would require that all vitamin preparations, including those of less strength, which were treated by the FDA as dietary supplements, be classified as drugs.

Since the record indicated that a significant number of persons, principally women taking oral contraceptives, used the higher dosage levels for nutritional purposes, Judge Friendly found that the record did not reveal sufficient evidence that such preparations were intended for therapeutic purposes to satisfy the "substantial evidence" standard, which controlled upon review of a regulation promulgated under § 701(e), and that the evidence of therapeutic intent or use must consist of "more than demonstrated uselessness [of the higher level forms] as a food for most people."

Since the Commissioner, in determining the "drug" status of the higher dosage levels of Vitamins A and D in this proceeding, appeared to rely heavily on the same record and conclusions that formed the basis for the regulation challenged in NNFA v. FDA, appellants argue that the determination here must *a fortiori* be invalidated. We disagree. We are here dealing with regulations which (1) differ in material respects from § 125.1(h), (2) were promulgated under a different statute, § 701(a), and (3) are subject to a less stringent standard of review. We are not, however, in a position to determine whether application of the lesser standard of review would yield the same result as that reached with respect to § 125.1(h), since we do not appear to have the Commissioner's complete reasoning behind his classification of the higher dosage levels as drugs. Nor does it appear that we have been furnished with the entire record that formed the basis of the FDA's classification.

12. "(h) Any product containing more than the upper limit of the U.S. RDA per serving (or, where appropropriate, per daily recommended quantity) of a vitamin or mineral as specified in § 80.1(f)(1) of this chapter is a drug, except for conventional foods which contain naturally-occurring amounts in excess of these limits or which contain added amounts in excess of these limits pursuant to § 1.8(e) of this chapter so that it is not nutritionally inferior to the food for which it substitutes and which it resembles, and except as provided for in a specific regulation for such special dietary foods as infant formulas or foods which are represented for use solely under medical supervision to meet nutritional requirements in specific medical conditions."

[17] Upon adoption of the regulations the Commissioner stated that since there was no evidence that the higher dosage levels were used for nutritional purposes except for use of Vitamin D by a limited number of persons with poor Vitamin D absorption needing up to 1,000 IU daily, they "are therefore appropriate only for therapeutic purposes and thus properly classed as drugs." As Judge Friendly said, "demonstrated uselessness as a food for most people" would not automatically establish that the higher levels qualify as a "drug" within the definition in § 201(g)(1). The statute requires a finding of intent that a product be used for therapeutic purposes, and the Commissioner made no such finding. However, in his earlier statement proposing the regulations here under review the Commissioner stated that "there is widespread promotion to the laity of excessive quantities of these vitamins for prophylaxis and treatment of a variety of diseases and disorders." This statement indicates that the Commissioner, upon promulgating the regulations, may not have fully stated his reasons for classifying the higher levels as drugs. It is conceivable, for instance, that the Commissioner had before him information demonstrating that the higher dosage forms were used almost exclusively for therapeutic purposes. Measuring intent on an objective basis, as it must be, he may have concluded that in view of the extremely small percentage used for nutritional purposes Vitamins A and D at higher dosage levels were intended for use in the "cure, mitigation, prevention or treatment of disease." In that case his action could hardly be arbitrary or capricious and the regulations could, consistently with NNFA v. FDA, be upheld.

Furthermore, there are several differences between the proceeding before the NNFA v. FDA court and that here. As to Vitamin A there is a difference between the upper level encountered in NNFA v. FDA (more than 8,000 IU) and that before us (more than 10,000 IU). Moreover, the present regulations, unlike § 125.1(h), specifically provide that one higher dosage form mentioned as being vended for nutritional purposes in NNFA v. FDA, i. e., Vitamin D up to 1,000 IU per dosage, may be used under medical supervision to meet nutritional requirements, provided it is so labelled. Unlike § 125.1(h), which declared on the basis of general reasoning that a broad range of vitamins and minerals are "drugs" when vended in dosages exceeding their RDA's, the regulations here are directed specifically at two vitamins, A and D. This suggests that the Commissioner may have engaged in a more detailed and specific consideration of these vitamins than was apparent in the § 125.1(h) proceeding. Finally, there appears to be evidence in the record, upon which the Commissioner may have relied, indicating that high potency vitamin products are labelled in such a way (e. g., "Take one a day or as *directed by a physician*") as to indicate a therapeutic use.

[18] Since the foregoing differences may prove to be significant, invalidation of the regulations here under attack is not automatically mandated by our decision in NNFA v. FDA. The situation is substantially similar to that encountered in Citizens to Preserve Overton Park v. Volpe, 401 U.S. 402, 91 S.Ct. 814, 28 L.Ed.2d 136 (1971), and the remedy prescribed by the Supreme Court in that case appears to be appropriate here. Accordingly we remand the case to the district court with directions to conduct an *Overton*-type hearing (including such affidavits or testimony as to the Commissioner's reasoning as the court deems necessary) for the purpose of determining whether, upon the entire administrative record before the Commissioner, which the court should scrutinize, Silva v. Lynn, 482 F.2d 1282 (1st Cir. 1973), the Commissioner acted rationally in classifying the higher Vitamin A and D dosage levels as a "drug" within the meaning of § 201(g) of the Act, 21 U.S.C. § 321(g). If the district court concludes that the Commissioner acted rationally, the regulations may be upheld and the order granting summary judgment should stand. The Commissioner's action in requiring that the higher dos-